Approaches to the Total Synthesis of the Complanadines

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APPROACHES TO THE TOTAL SYNTHESIS OF THE COMPLANADINES

A Thesis Presented by

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…….. ……

Mario Uosis-Martin Date

Dedicated to my mother.

Skiriu mamai.

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IV. ACKNOWLEDGEMENTS

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V. ABSTRACT

In this thesis is presented work carried out during the course of the last 42 months. It concerns approaches towards total syntheses of the complanadine alkaloids. The main focus is the development of a model system to establish the viability of the key step in our proposed route to the complanadines. The thesis is divided into five chapters.

Chapter 1 is an introduction to the complanadines, their biological activity and accomplished total syntheses to date. A brief introduction to the Diels–Alder reaction and selected examples of its application in the total syntheses of natural products are given. The Kondrat'eva oxazole–olefin hetero-Diels–Alder reaction as a method of pyridine formation is described and its application in the total synthesis of natural products is reviewed.

Chapter 2 is the first part of the results and discussion section. It details our retrosynthetic analysis of complanadine A, outlines the corresponding proposed forward synthesis and presents a model system designed and synthesised to test the applicability of the Kondrat'eva oxazole–olefin hetero-Diels–Alder reaction in the context of our proposed total synthesis.

Chapter 3 discusses work carried out in approaches to the total synthesis of complanadines and their monomeric subunit, lycodine, by means of the methodology developed in the previous chapter.

Chapter 4 is the experimental section, which gives descriptions of the synthetic procedures employed and spectroscopic data for all compounds synthesised, both novel and previously reported, as discussed in Chapter 2 and Chapter 3.

Supplementary information such as X-Ray data for synthesised compounds and selected NMR spectra are enclosed in the appendices.

VI. ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
Å	angstrom
AcOH	acetic acid
AIBN	2,2'-azobis(2-methylpropionitrile)
app	apparent
aq	aqueous
Ar	aromatic
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
b.pt.	boiling point
BQ	1,4-benzoquinone
br	broad
BTSP	1,3-bis(trymethylsiloxy)propane
Bu	butyl
^{n}Bu	*normal*-butyl
^{n}BuLi	*normal*-butyl lithium
℃	degrees celsius
cat.	catalytic quantity
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
$CDCl_3$	chloroform-d
conc.	concentrated
COSY	correlation spectroscopy
$Cu(OTf)_2$	copper (II) triflate
δ	chemical shift in parts per million
Δ	reflux
d	doublet
DCB	dichlorobenzene
DBN	1,5-diazobicyclo[4.3.0]non-5-ene
DBU	1,8-diazobicyclo[5.4.0]undecen-7-ene

DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
DEG	diethyleneglycol
DIBAL-H	diisobutylaluminium hydride
DIC	diisopropyl carbodiimide
DIE	1,2-diiodoethane
dil.	dilute
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DNPH	2,4-dinitrophenylhydrazine
dppf	diphenylphosphino ferrocene
dt	doublet of triplets
EBDPP	ethylenebis(diphenylphosphine)
EDG	electron donating group
equiv.	equivalent(s)
ES	electrospray
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOH	ethanol
$Eu(fod)_3$	Europium(III) tris(6,6,7,7,8,8,8,-heptafluoro-2,2-dimethyl-3,5-octanedionate
EWG	electron withdrawing group
FGI	functional group interconversion
g	gram
h	hour(s)
Hz	Hertz
HWE	Horner–Wadsworth–Emmons reaction

i	*iso*
IR	infrared
IMDA	intramolecular Diels–Alder reaction
J	coupling constant
LA	Lewis acid
LG	leaving group
m	*meta*
m	multiplet
M	molar
Me	methyl
Mes	mesityl; 2,4,6-trimethylphenyl
mg	milligram
MHz	mega Hertz
mmol	millimole
min	minute(s)
mL	millilitre
µL	microlitre
m.pt.	melting point
Ms	methanesulfonyl; mesyl
MS	molecular sieves, mass spectrometry
MW	molecular weight
µW	microwave
m/z	mass to charge ratio
$NaBH_4$	sodium borohydride
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
o	*ortho*
o	octet
(P)	protecting group
p	*para*
Ph	phenyl

PMA	phorbol myristyl acetate
PMB	*p*-methoxybenzyl
PNB	*p*-nitrobenzyl
ppm	parts per million
Pr	propyl
p-TSA	*p*-toluenesulfonic acid
q	quartet
R	generic substituent
rt	room temperature
s	singlet
sat.	saturated
SET	single electron transfer
sol.	solution
t	triplet
td	triplet of doublets
TBAF	tetrabuthylammonium fluoride
TBDMS	*tert*-butyldimethyl silyl
TBDMSCl	*tert*-butyldimethyl silylchloride
TCDI	1,1'-thiocarbonyldiimidazole
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluene
TPP	tetraphenylporphyrin; 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine
Ts	tosyl; *para*-toluenesulfonyl
w/up	workup
$Yb(OTf)_3$	ytterbium (III) triflate
ν	wavenumber

Chapter 1

Introduction

1. INTRODUCTION

1.1 Alkaloids

Alkaloids are a class of secondary metabolites which contain one or more basic nitrogen functional group and which occur in plants, microorganisms, marine organisms, and animals. Plants are estimated to produce approximately 40,000 different alkaloids, which can be organized into groups according to their carbon skeletal structures. The role of these compounds in plants is not always clear and can vary, however it is believed they play a part in plant defence against herbivores, to improve their growth, reproduction and survival.[1] For example, liriodenine (**1**) shows antifungal activity protecting the plant from parasitic fungi (Figure 1.1).[2] In contrast, alkaloid substances such as serotonin (**2**) play a vital role in neurotransmission in animals including humans.[3]

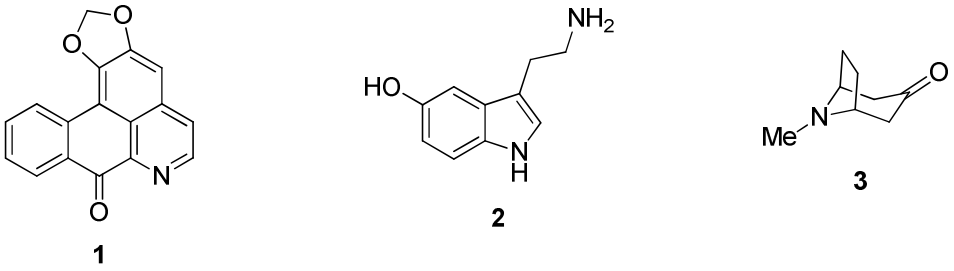


Figure 1.1 Structures of liriodenine, serotonin and tropinone.

As the number of alkaloids identified has increased, so has the number of alkaloid families into which they are classified. Like other natural products, biosynthesis of alkaloids in plants involves complicated multi-step pathways and is catalysed by enzymes. The identification and characterization of novel alkaloid biosynthetic enzymes has been the focus of much research over the past few decades. Although it is not always clear why certain alkaloids show

significant biological activity, they are often useful as drugs or as biological probes for physiological studies. Interest in the importance of biologically active alkaloids has increased due to their potential application in medical treatment of various conditions. Since the synthesis of tropinone (**3**) by Robinson[4] in 1917, generations of chemists have been looking into the realisation and development of total syntheses of these challenging natural products .

1.2 The Complanadines

Lycopodium alkaloids[5] represent a large family of plant substances obtained from club mosses belonging to the *Lycopodiaceae* family. These structurally diverse alkaloids often possess unusual skeletal connectivity. Many of them continue to be of interest from medicinal and biological points of view, as well as providing challenging targets for synthetic chemists. New natural compounds belonging to this group have been isolated in the last decade, including the complanadines (Figure 1.2).[6-8]

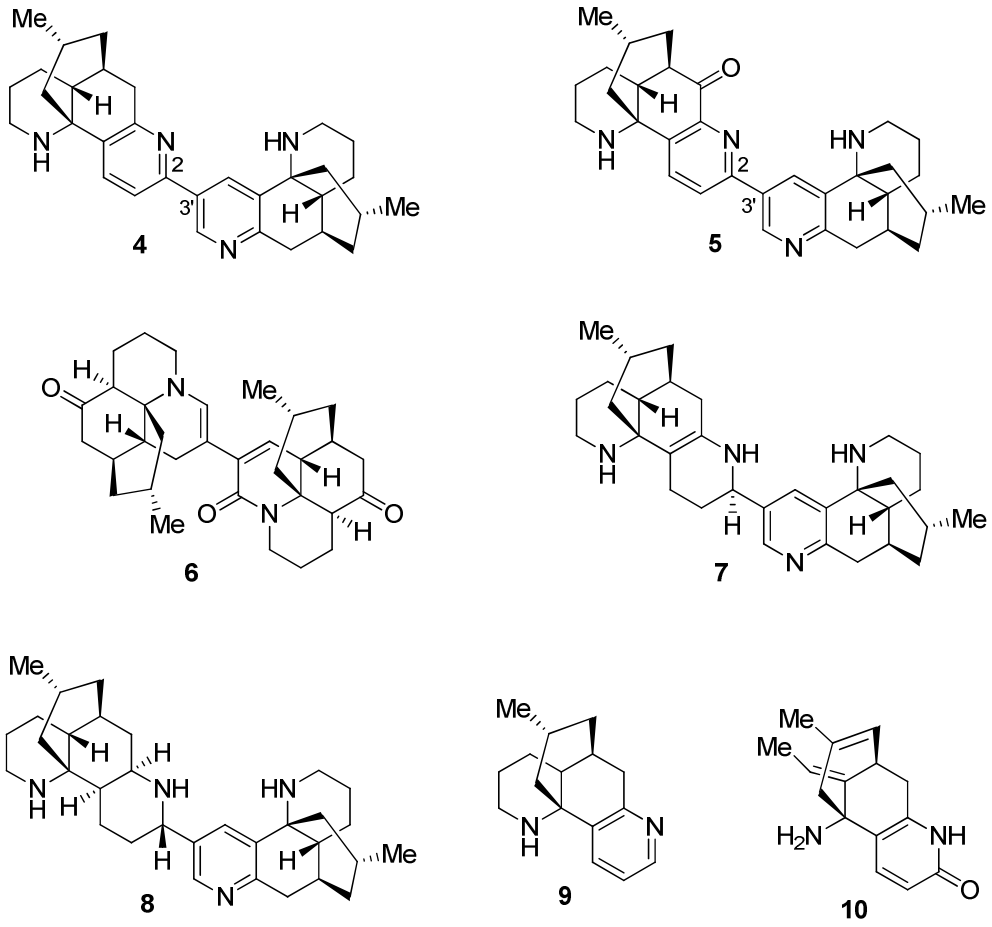


Figure 1.2 Complanadines A-E, lycodine and huperzine A.

The first, complanadine A (**4**)[7], was reported by Kobayashi *et. al*. in 2000, and was followed by the isolation of complanadine B (**5**)[8] in 2005, complanadines C (**6**)[6] & D (**7**)[6] in 2007 and complanadine E (**8**)[9] in 2011. As shown in Figure 1.2, **4**, **5, 7** and **8** are dimeric derivatives of the known tetracyclic alkaloid lycodine (**9**)[5], varying only in oxidation state, whereas derivative **6** has different skeletal connectivity.

Intriguingly, **4**, **5**, **7** and **8** all possess a non-symmetric 2,3'-bipyridyl type linkage, a rare alkaloid structural motif. Complanadines A **4** and D **7** show moderate cytotoxicity towards murine leukemia L1210 cells[6,7] whereas complanadine C **3** does not. Also, complanadines C **6** and D **7** show antimicrobial activity towards *Cryptococcus neoformans* and *Aspergillus niger*.[6]

Perhaps most significant, however, are the reported neurotrophic effects of **4**, **5** and **6**.[6,8] These have been studied in the most detail for complanadine A **4**, which was reported to induce neurite outgrowth of PC-12 cells in a dose-dependent manner (Figure 1.3). To date there are no available biological data for complanadine E **8**.

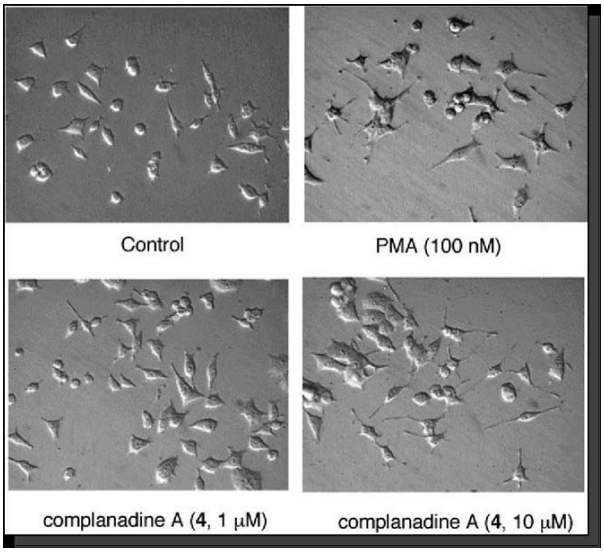


Figure 1.3 Glial cell-mediated morphological change of PC-12 cells by complanadine A, reproduced from reference 8.

Compounds able to induce neuronal differentiation and neurite outgrowth are of medicinal interest as potential treatments for neurodegenerative conditions. Indeed, the related lycopodium alkaloid huperzine A (**10**)[5] has been used for the treatment of Alzheimer's disease in traditional chinese medicine for many years.

1.3 The Lycopodium Alkaloids

Complanadines belong to the lycopodium alkaloid family, a diverse group of natural products generally consisting of sixteen carbon and one or two nitrogen atoms, with various degrees of oxygenation. They are presumably derived from

two 2-propylpiperidine subunits (Figure 1.4). Ma and Gang[5] recently reviewed the chemical, pharmacological, and clinical research being performed on this family of alkaloids, and several previous reviews exist as well.[10,11]

The lycopodium family is often divided into four classes based on their structural skeletons. These classes are the lycodines, the lycopodines, the fawcettimines, and a miscellaneous class.[5] A typical example from each of these classes is shown in Figure 1.4, where phlegmarine (**11**) is the example of the miscellaneous class. Although the biosynthesis of the lycopodium alkaloids is not completely understood, it is thought that phlegmarine **11**, in which the two 2-propylpiperidine subunits (highlighted in red and purple) (Figure 1.4) are more obvious, is the common precursor to all classes of the lycopodium alkaloids. Thus, bond formation between C-4 and C-13 of phlegmarine yields the lycodine **9** skeleton. From lycodine, disconnection of the C-1–N_α bond, and reconnection of C-1 to N_β gives the lycopodine structure (**12**). From there, migration of C-4 from C-13 to C-12 reveals the fawcettimine (**13**) skeleton.

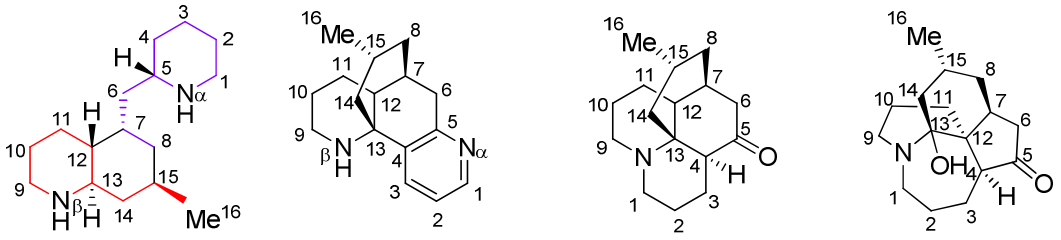


Figure 1.4 Representative compounds of the major classes of lycopodium alkaloids.

Many representatives of the lycopodium family are biologically active. For example, a feature of many compounds in the lycodine subclass is their ability to inhibit acetylcholinesterase.[12] Of these, huperzine A **10** is the most potent.[13,14] It has been shown that due to its strong inhibition of acetylcholinesterase it increases memory and learning efficiency in mammals,[13,14] and shows promise in the treatment of Alzheimer's disease and

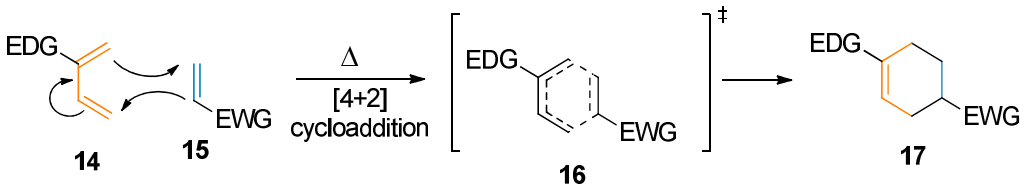
an autoimmune neuromuscular disease known as myasthenia gravis.[15] Huperzine A and a Schiff base derivative of huperzine A named ZT-1 are currently in clinical trials for use as a treatment for Alzheimer's disease.[5]

1.4 The Diels–Alder Reaction

The most widely applied pericyclic reaction for the construction of six-membered functionalised carbocyclic or heterocyclic compounds is the Diels–Alder reaction. The usefulness of this [4+2] cycloaddition reaction is especially valuable in cases of structurally complex natural product targets. This arises from its high regio- and stereoselectivity and its versatility, as wide range of dienes and dienophiles can be used.

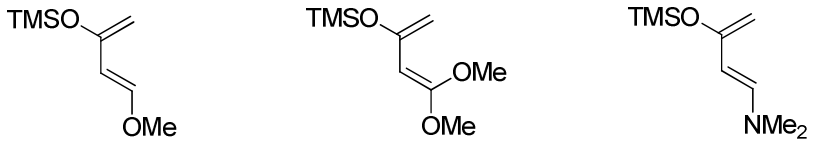
This reaction was first documented in 1928 by Otto Paul Hermann Diels and his student Kurt Alder.[16] In 1950, for their work on this reaction, Diels and Alder were awarded the Nobel prize in chemistry.[17]

The reaction between a conjugated diene (**14**) and a substituted alkene (**15**), commonly termed the dienophile, occurs *via* single transition state (**16**) (Scheme 1.1), to form a cyclic adduct (**17**) with the formation of two new σ-bonds at the expense of two π-bonds in the starting reagents. It is an associative type of reaction, and it is accelerated by high temperatures or pressures.



Scheme 1.1 Simplified Diels–Alder reaction scheme.

The majority of these reactions involve electron-rich dienes possessing electron donation groups such as alkyl or alkoxy and electron-poor dienophiles activated by electron withdrawing groups (carbonyls, -CF_3, -CN). The most commonly known activated dienes are Danishefsky's diene (**18**) and the similar Danishefsky-Brassard (**19**) and Rawal's dienes (**20**) (Figure 1.5).



18 **19** **20**

Figure 1.5 Electron-rich dienes.

1.4.1 Frontier Molecular Orbitals and the Diels–Alder reaction

According to frontier orbital theory, it is possible to determine if a pericyclic reaction is allowed or forbidden by simply considering the relationship of the frontier orbitals of the reactants. The frontier orbitals are the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The interaction between these orbitals, a so-called HOMO-LUMO interaction, is a concept that is similar to Lewis acid-Lewis base chemistry, which involves the interaction of a filled orbital of the base with an empty orbital of the acid. According to this theory, a pericyclic reaction is allowed when the HOMO of one reactant has the same symmetry as the LUMO of the other.

Returning to the Diels-Alder reaction, 1,3-butadiene has four π orbitals, ψ_{1A}, ψ_{2A}, ψ_{3A} and ψ_{4A}, with ψ_{2A} being the HOMO. Ethylene has two π orbitals which are labelled ψ_{1B} and ψ_{2B}, the latter being the LUMO (Figure 1.6). Figure 1.6 shows an idealized geometry for the approach of these frontier orbitals in parallel planes. The black dashed lines highlight the initiative overlap of the terminal lobes of the 4π electron system of the diene and 2π electron system of

the dienophiles. This is the origin of the "[4+2]" nomenclature for the cycloaddition. Since the HOMO-LUMO interaction shown in (Figure 1.6) involves orbitals of the same symmetry, the reaction is allowed; the interaction is suprafacial on both components.

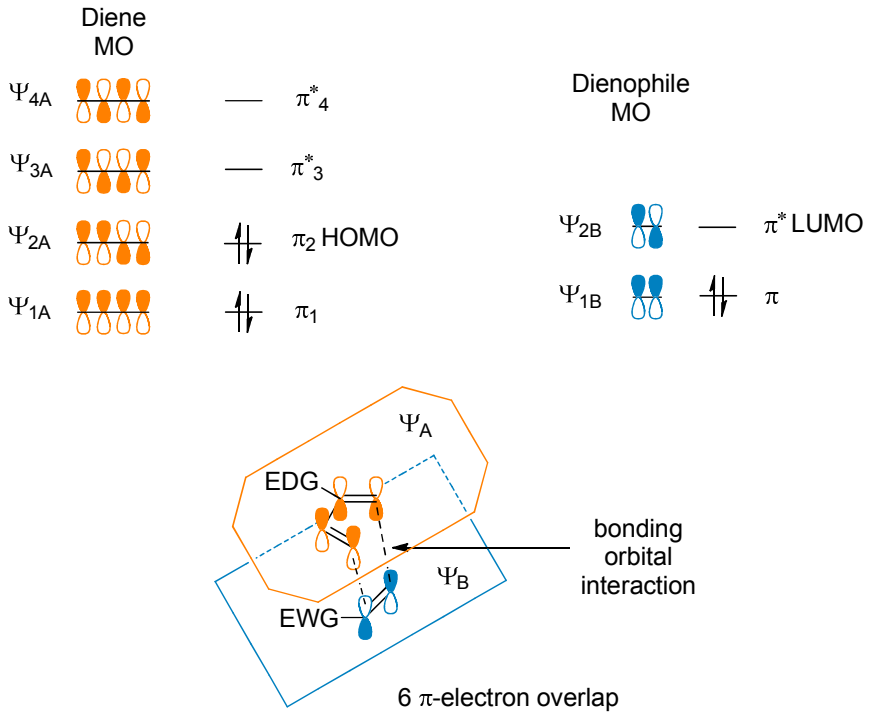
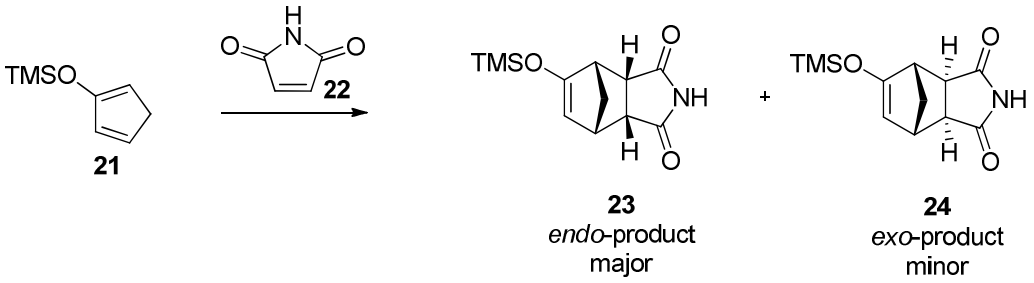


Figure 1.6 Frontier molecular orbital diagram for diene and dienophile, and 6 π electron overlap.

In an example of a Diels–Alder reaction of (**21**) with (**22**) we can see the reaction can proceed deriving the *endo*-product (**23**) and the *exo*-product (**24**) (Scheme 1.2).



Scheme 1.2 An example of Diels–Alder reaction.

Endo and *exo* selectivity is an important consideration in certain Diels–Alder reactions. The *exo* approach would afford the thermodynamically favoured product, whereas the *endo* approach would afford the kinetically favoured product. The *endo* adducts are normally the observed products, which can be explained by secondary orbital interactions, shown as red dashed lines (Figure 1.7).

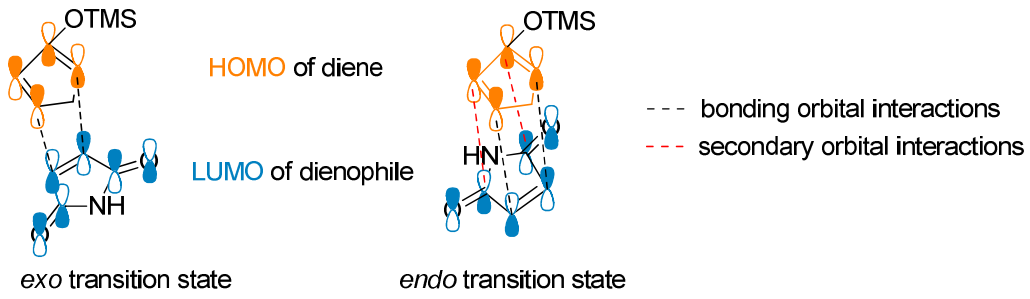


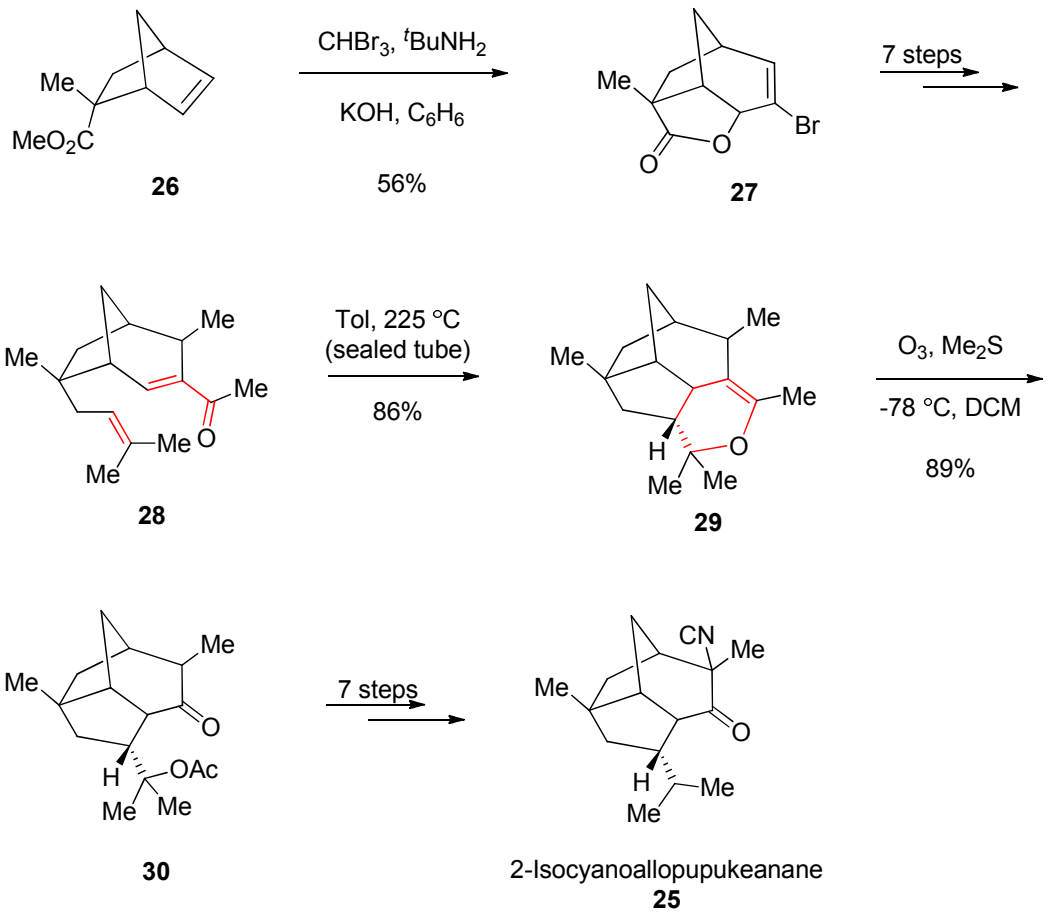
Figure 1.7 Bonding orbital interactions and secondary orbital interactions diagram.

1.4.2 Applications Of The Diels–Alder Reaction In The Total Synthesis Of Natural Products

Some significant total syntheses of natural products such as terpenoids, steroids, alkaloids and polyketide-derived natural products, have been achieved based on the IMDA reaction.[18]

1.4.3 The Diels–Alder Reaction In The Total Synthesis Of Isocyanopupukeanane Terpenoid

2-Isocyanoallopupukeanane (**25**) belongs to a class of structurally unique marine sesquiterpenoids called isocyanopupukeananes. Ho *et al.*[19] used the intramolecular hetero-Diels–Alder reaction as a key step in the total synthesis of (±)-**25** (Scheme 1.3).



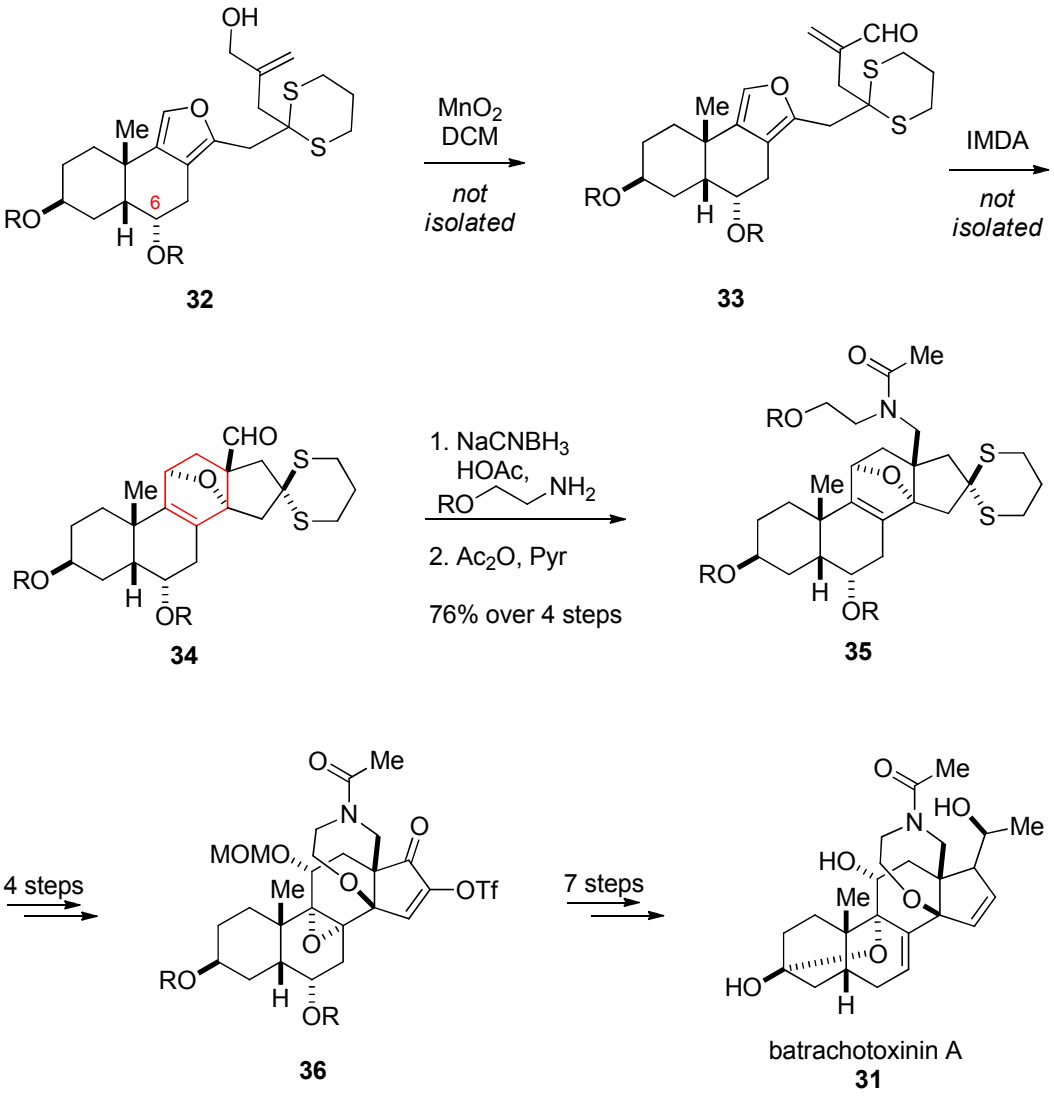
Scheme 1.3 Total synthesis of 2-isocyanoallopupukeanane.

The addition of dibromocarbene to a 5-norbornene-2-carboxylic acid ester (**26**) induced a ring expansion to provide tricyclic lactone (**27**), which was elaborated to bicyclo[3.2.1]oct-2-ene (**28**), possessing an α,β-unsaturated ketone and a 2-

methylbutenyl unit as a hetero-diene and a dienophile, respectively. When **28** was heated, the intramolecular hetero-Diels–Alder reaction proceeded to afford cycloadduct (**29**) with the tricyclic framework required for the further steps in the synthesis of isocuanoallopupukeanane. Next, the alkene moiety in **29** was cleaved by ozonolysis to give (**30**). With seven more synthetic operations from **30**, including the introduction of an isocyano group, the total synthesis of (±)-**25** was successfully accomplished.

1.4.4 The Diels–Alder Reaction In The Total Synthesis Of Batrachotoxin Steroid

The batrachotoxins are a unique class of steroidal alkaloids, isolated in minute quantities from the skins of poison arrow frogs and they have been isolated from the feathers of a New Guinea bird. Kishi and co-workers[20] have achieved the total synthesis of (±)-batrachotoxinin A (**31**) by using an intramolecular furan Diels–Alder reaction (Scheme 1.4).



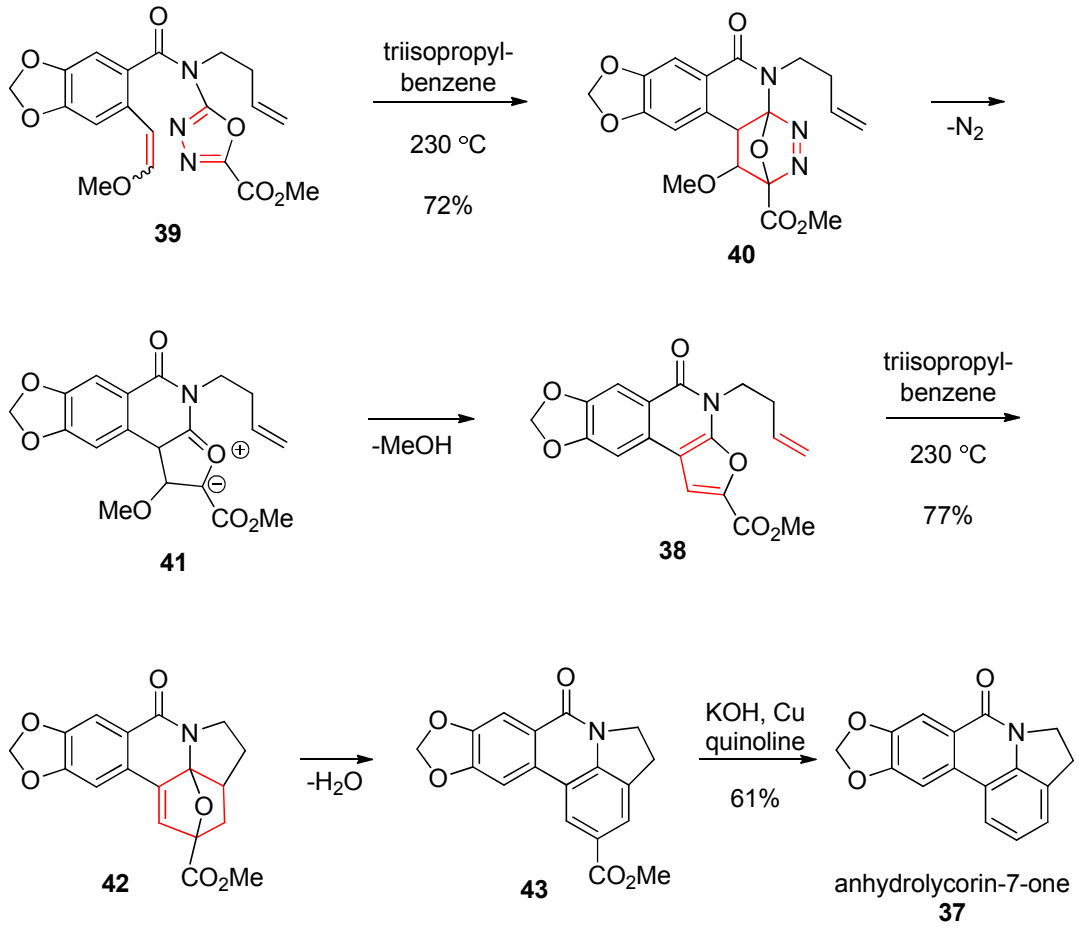
Scheme 1.4 Total synthesis of batrachotoxinin A.

The synthetic precursor (**32**) of the substrate (**33**) for the attempted IMDA reaction was prepared efficiently from (±)-Wieland–Miescher ketone.[21] The allylic alcohol **32** was oxidized to terminal enal **33** with MnO_2, which smoothly underwent an intramolecular [4+2] cycloaddition with the furan moiety. The resulting cycloadduct (**34**), obtained highly stereoselectively, was directly subjected to reductive amination and then acetylation, affording a single product (**35**) in good yield.

The stereoselectivity of the IMDA reaction was dramatically influenced by the C6 substituent (an OTBDMS group). In fact, a C6 deoxy analogue provided the corresponding cycloadduct in 3-4:1 diastereoselectivity, while the C6 β-OPMB derivative underwent [4+2] cycloaddition with poor (3:2) selectivity. The cycloadduct **35** was then transformed into (**36**) *via* an intramolecular oxy-Michael reaction. After further functional group manipulations, (±)-**31** was eventually synthesised.

1.4.5 The Diels–Alder Reaction in the Total Synthesis Of Anhydrolycorin-7-one

Boger *et al.* reported the total synthesis of anhydrolycorin-7-one (**37**), by application of one-pot 2-fold IMDA reactions of 2-amino-1,3,4-oxadiazoles (Scheme 1.5). The Boger group[22] developed the IMDA reactions of 2-amino-1,3,4-oxadiazoles, tethering an alkenyl functionality, which serves as a dienophile. This elaborate strategy was effectively used for the total synthesis of **37**. Thus, the IMDA substrate was subjected to thermal conditions for the construction of an advanced intermediate (**38**) in a single step by heating an *N*-functionalized 2-amino-1,3,4-oxadiazole-5-carboxylate (**39**). The initial [4+2] cycloaddition afforded heterocyclic adduct (**40**), which underwent the loss of nitrogen to generate a carbonyl ylide (**41**). This zwitterionic intermediate then aromatized through elimination of methanol, furnishing a furan intermediate **38**. Then 2-amidofuran **38** underwent a similar IMDA reaction to give (**42**), followed by aromatization with the removal of water, eventually providing (**43**). The conversion of **43** into **37** was achieved by decarboxylation. The Boger group employed analogous sequential IMDA reactions of *N*-acyl-6-amino-1,2,4,5-tetrazine in the total syntheses of anhydrolycorin-7-one[23] and hippadine[23].



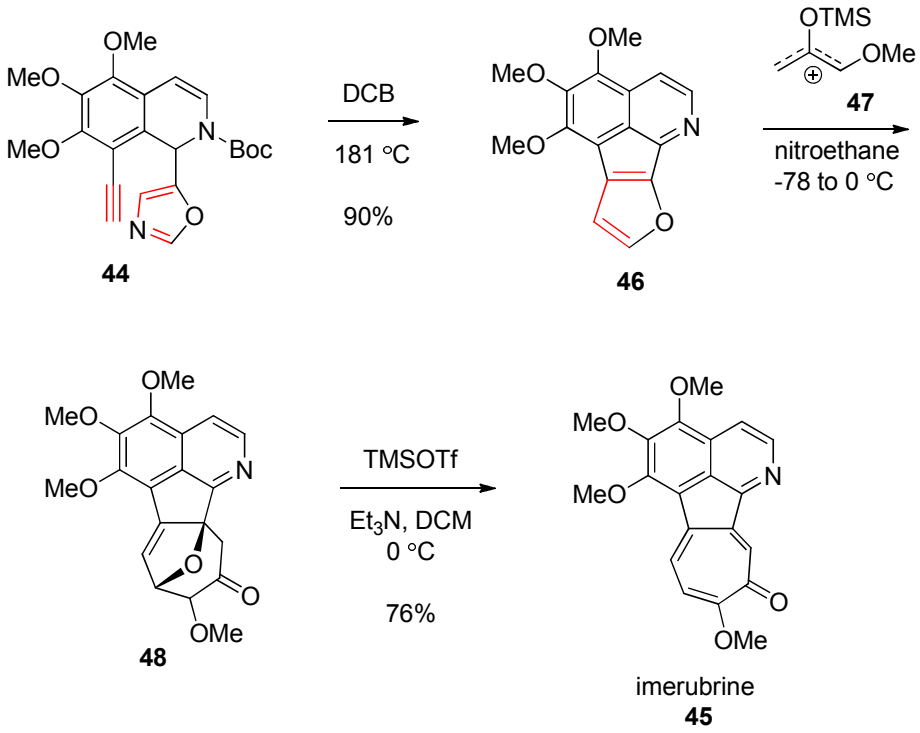
Scheme 1.5 The total synthesis of anhydrolycorin-7-one.

1.4.6 The Diels–Alder Reaction in the Total Synthesis Of Imerubrin Alkaloid

Lee and Cha[24] have used the IMDA reaction of an acetylene-containing isoquinoline-derived oxazole (**44**) in their total synthesis of imerubrine (**45**) (Scheme 1.6) which belongs to the tropoloisoquinoline alkaloid family. The IMDA reaction of the substrate **44**, which is followed by a retro-Diels–Alder reaction with the elimination of hydrogen cyanide, provided a tetracyclic compound (**46**) after the simultaneous removal of the Boc group. Remarkably

this cyclization–elimination cascade proceeds smoothly in a one-pot operation under thermal conditions in good yield.

The key [4+3] cycloaddition reaction was achieved by reaction of **46** with α-methoxy trimethylsyloxyallyl cation (**47**) generated *in situ* from ((3,3-dimethoxyprop-1-en-2-yl)oxy)trimethylsilane by reaction with TMSOTf in nitroethane to furnish cycloadduct (**48**). The same group has also reported the total synthesis of (–)-colchicine, a related tropolone alkaloid, using a similar strategy.[25]

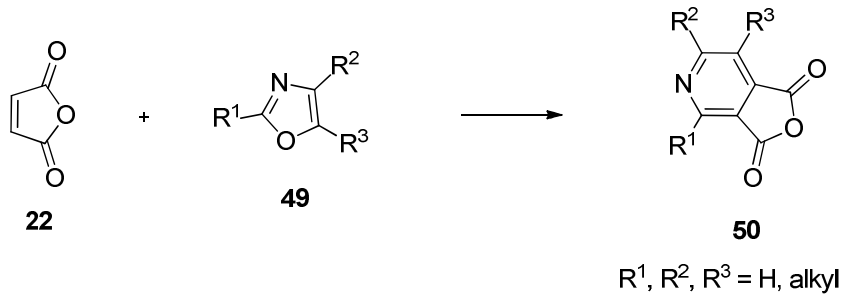


Scheme 1.6 The total synthesis of imerubrine.

1.5 Kondrat'eva Oxazole-Olefin Diels–Alder Reaction

The Diels–Alder reaction of oxazoles with alkenes is a valuable tool for the construction of highly substituted pyridines and it has been exploited for the synthesis of numerous compounds, from complex natural products to application in the synthesis of pharmaceuticals.

Kondrat'eva was the first to report the use of an oxazole as an azadiene in a Diels–Alder reaction.[26,27] The report presented seminal studies on a variety of alkyl-substituted oxazoles (**49**) and their reactions with maleic acid anhydride **22** in either benzene or ether to provide the cycloaddition products (**50**) (Scheme 1.7).



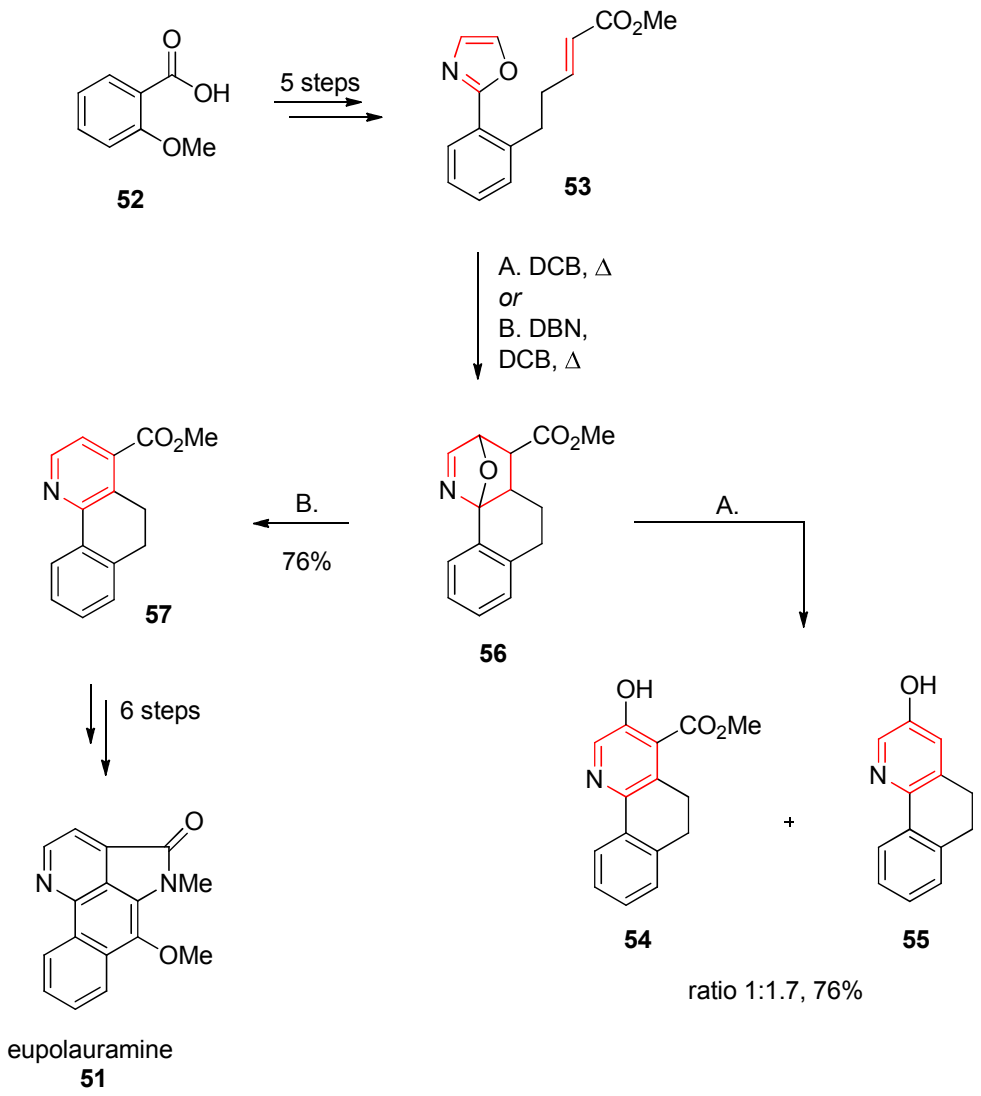
Scheme 1.7 First application of oxazole as azadiene in Diels–Alder reaction by Kondrat'eva.

Unlike the reaction of oxazole with alkynes, this reaction furnished highly substituted pyridines instead of furans. This reaction attracted the interest of many synthetic chemists and since the publication of Kondrat'eva in 1975 it has been applied in the syntheses of various pyridine-containing natural products.

1.5.1 The Kondrat'eva Oxazole–Olefin Diels–Alder Reaction: Applications In Total Synthesis

Despite an early recognition of practical value of the Kondrat'eva oxazole-olefin Diels–Alder reaction, there are few reports applying this cycloaddition in an *intramolecular* fashion to the synthesis of pyridine-containing natural products.

The first report of an intramolecular Diels–Alder cycloaddition of an oxazole with an alkene in the context of total synthesis was from Weinreb and Levin[28] at Pennsylvania State University. As a target to test the feasibility of the IMDA cycloaddition, they chose the unusual azaphenanthrene alkaloid eupolauramine (**51**). As starting materials, *o*-anisic acid (**52**) and ethanolamine were used. The oxazole intermediate (**53**) was achieved in 5 steps. Unsaturated ester **53** then was refluxed under nitrogen for 3 h at 0.014 M in DCB. Two tricyclic hydroxypyridines (**54**) and (**55**) were obtained in a 1:1.7 ratio in 67% total yield (Scheme 1.8).



Scheme 1.8 The total synthesis of eupolauramine.

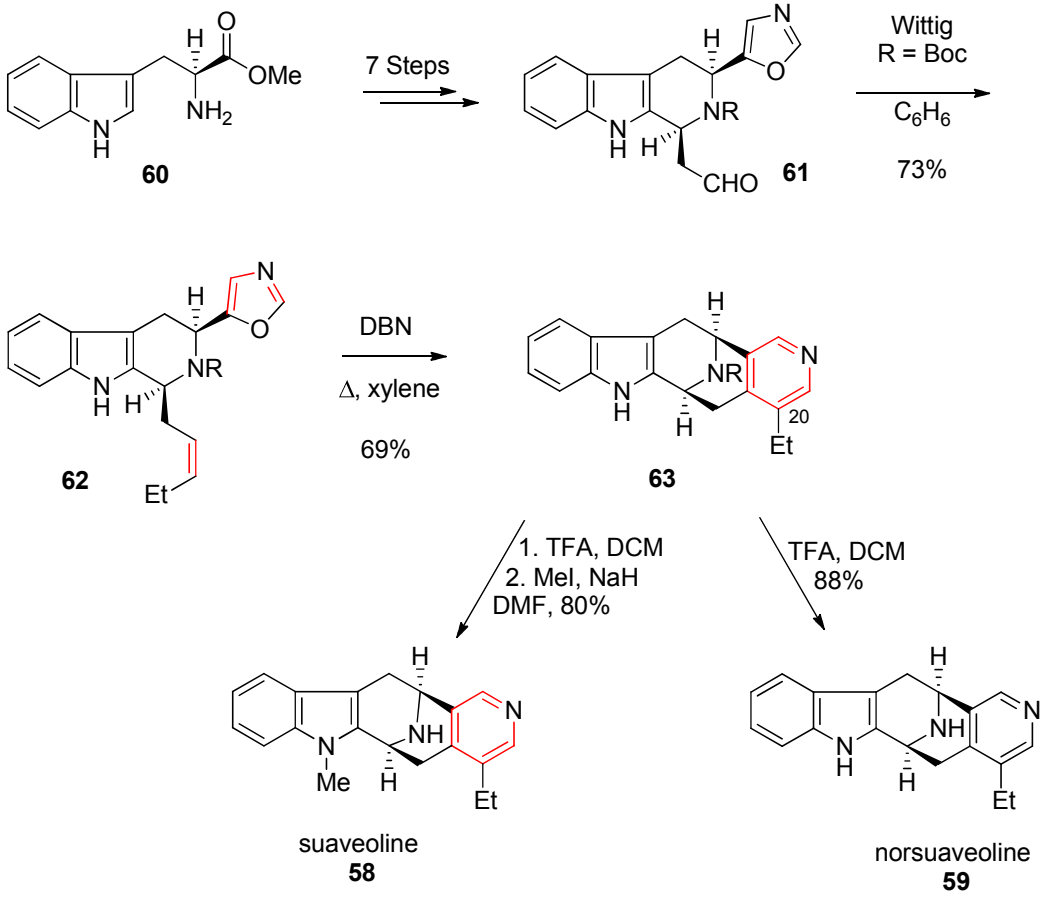
Compounds **54** and **55** probably arise *via* Diels–Alder adduct (**56**) which undergoes oxidative fragmentation through the hydride elimination pathway. Weinreb and Levin had an initial assumption that either traces of oxygen which were present during the IMDA reaction and/or the solvent itself were responsible for the oxidative fragmentation of the cycloadduct **56**. Thus, cycloaddition reactions were performed using ethylbenzene, bromobenzene, and *o*-dichlorobenzene as a solvent after thoroughly degassing each with argon. In every case, however, the 3-hydroxypyridines **54** and **55** were the sole

products of the IMDA reactions. The only effect of changing solvent appeared to be a decrease in the relative amount of the decarboxylated pyridinol **55** obtained when the reaction was run at a lower temperature. For example, the ratio of **54** to **55** changed to 4.4:1 (70% total yield) when bromobenzene was used as the reaction solvent. It would appear the oxygen is at least partly responsible for the oxidative decomposition of cycloadduct **56**. In the absence of oxygen the Diels–Alder adduct must follow other degradative pathways, possibly involving disproportionation.

In 1968 Colin patented a synthesis of isonicotinic acid esters and isonicotinonitriles *via* the Diels–Alder reaction of oxazoles with acrylic esters or acrylonitrile in the presence of triethylamine.[28] It seemed reasonable that the triethylamine might function by accelerating the elimination of water from the initially formed Diels–Alder cycloadduct. Weinreb and Levin reasoned that the use of a non-nucleophilic base in the Diels–Alder reaction of compound (**57**) might increase the rate of the loss of water from cycloadduct **56** relative to that of the oxidative fragmentation, thereby providing the desired annelated pyridine **57** instead of 3-hydroxypyridines. Indeed, when Diels–Alder precursor **53** was refluxed in *o*-dichlorobenzene for 16 h with 0.75 equivalents of 1,5-diazabicyclo[4.3.0]non-5ene, only the desired tricyclic pyridine ester **57** was produced in 76% yield.

Ohba and co-workers[29] have achieved the total synthesis of the *Rauwolfia* alkaloids suaveoline (**58**) and norsuaveoline (**59**) using the Kondrat'eva reaction (Scheme 1.9). To achieve the synthesis of suaveoline and norsuaveoline, which have an ethyl group at the 20-position, the authors used a commercially available amino ester (**60**). Over 7 steps the aldehyde (**61**) was prepared and then a Wittig reaction was carried out using the phosphorane prepared from *n*-propyltriphenylphosphonium bromide and *t*-BuOK, furnishing the (*Z*)-olefin (**62**) in a good yield. Addition of $Cu(OTf)_2$ failed to give cyclisation product due to rapid decomposition, although the same group reported that this Lewis acid promoted a comparable cycloaddition leading to cyclopenta[*c*]pyridines.[30] However, treatment of the olefin **62** in DCB at 160 ^{o}C in the presence of 1.50

equiv. of 1,5-diazabicyclo[4.3.0]non-5ene, an application of Weinreb's procedure, improved slightly the yield of the product. Furthermore, alteration of the solvent from DCB to xylene raised the yield of cycloaddition product to 50%. By the use of 5.00 equiv. of 1,5-diazabicyclo[4.3.0]non-5ene, the pyridine (**63**) was obtained in 65% yield. Ultimately, treatment of the key intermediate **62** with 20.00 equiv. of 1,5-diazabicyclo[4.3.0]non-5ene in refluxing xylene gave desired pyridine **63** in 69% yield as the best result. It is likely that 1,5-diazabicyclo[4.3.0]non-5ene might serve as a scavenger of water and promote the conversion of the initially formed Diels–Alder cycloadduct into the pyridines.



Scheme 1.9 Total synthesis of suaveoline and norsuaveoline.

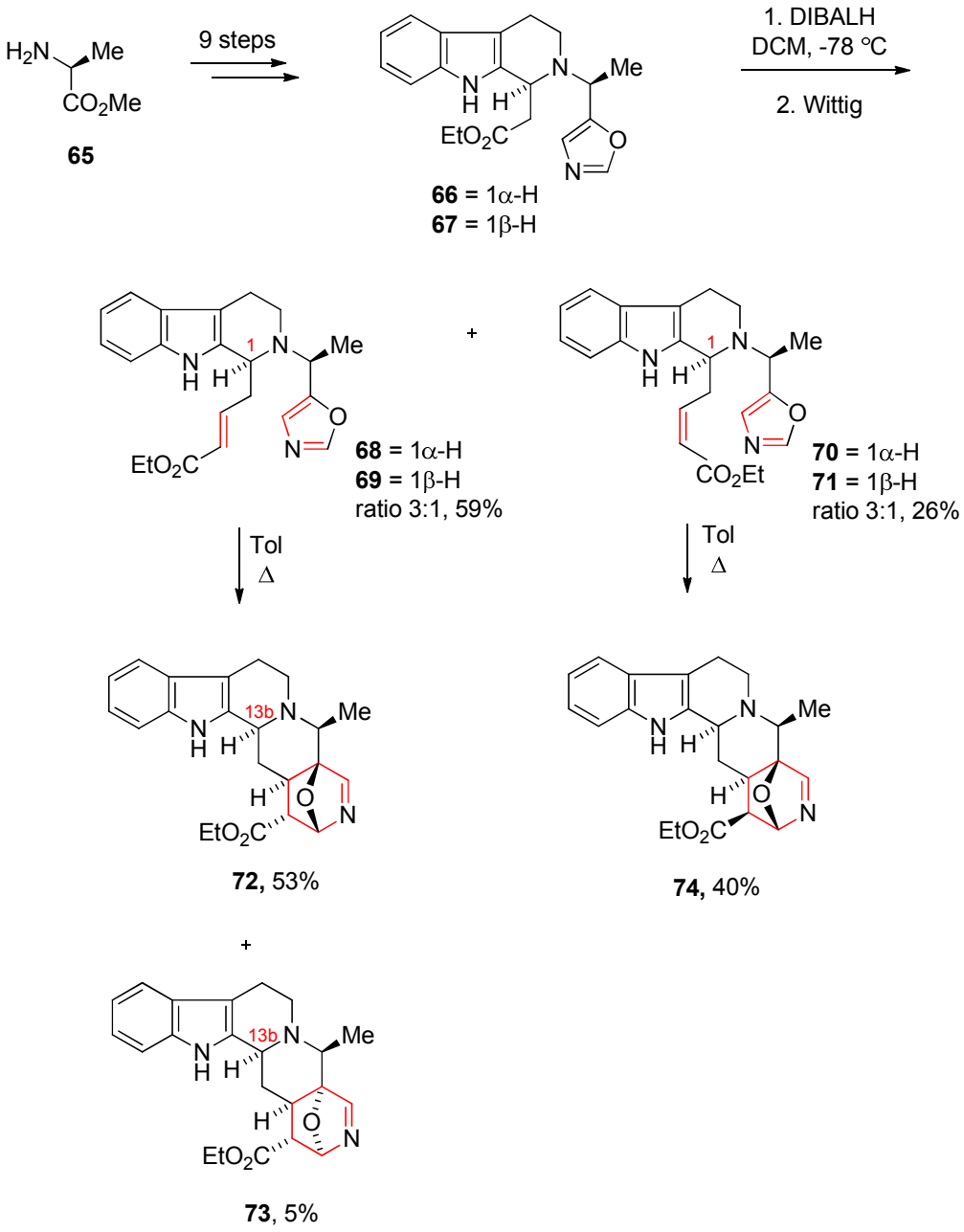
Methylation of **63** with MeI was performed in the presence of NaH in DMF, affording the indole N_α-Me derivative and finally removal of the Boc protecting

group in trifluoroacetic acid gave target compound **58** in 82% yield and deprotection of **63** gave norsuaveoline in 88% yield.

(–)-Normalindine (**64**) was reported for the first time as one of the many alkaloids isolated from the root bark of *Strychnos johnsonii* (Loganiaceae) by Massiot *et al.* in 1987.[31] The initial step in its subsequent total synthesis by Ohba *at al.* was *N*-alkylation of L-alanine methyl ester (**65**) with 2-(3-indolyl)ethyl bromide (Scheme 1.10). The amino esters (**66**) and (**67**) were obtained as a 3:1 diastereomeric mixture over 8 steps.[32,33]

With a view to introducing an olefinic dienophile into the amino esters **66** and **67**, the above 3:1 mixture was treated with DIBAL-H at –78 °C in DCM, followed by the Wittig reaction with ethyl(triphenylphosphoranylidene)acetate in a one-pot procedure. A 3:1 mixture of the (*E*)-esters (**68**) and (**69**) and a 3:1 mixture of (*Z*)-esters (**70**) and (**71**) were obtained in 59% and 26% overall yields.

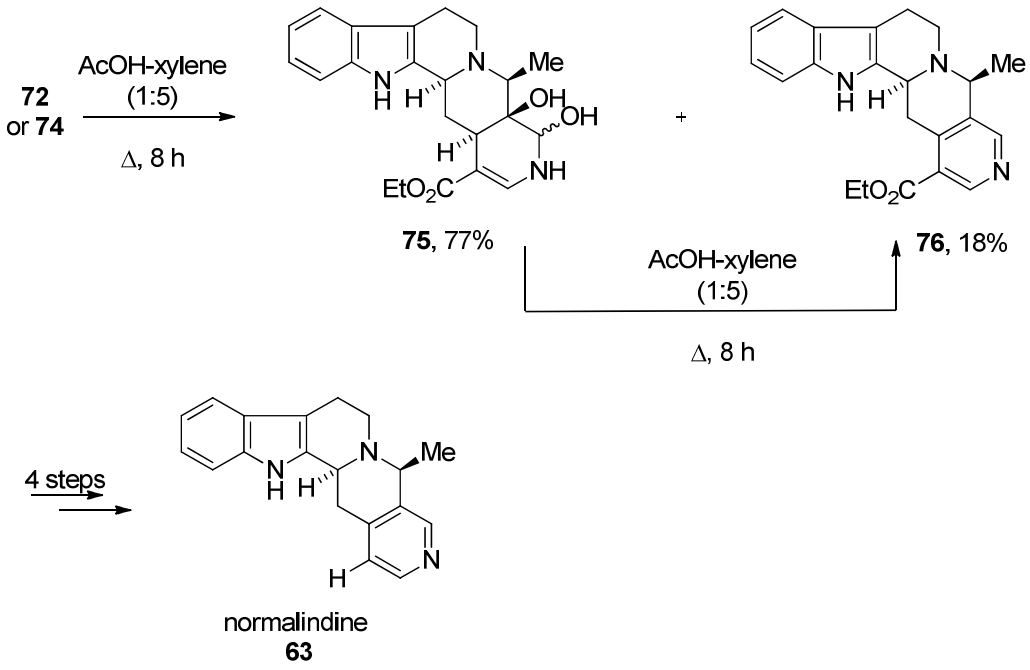
After successful syntheses of the oxazole-olefin derivatives, the group explored IMDA reactions. The best result was obtained by heating the 3:1 mixture of (*E*)-isomers **68** and **69** in refluxing toluene for 24 h. Under these conditions, the adducts (**72**) and (**73**), both having *α*- configuration for the C(13b) proton, were produced in 53% and 5% yields, respectively. Addition of Lewis acids such as $Eu(fod)_3$ and $Yb(OTf)_3$, failed to improve the yields of the adducts **72** and **73**.



Scheme 1.10 Key step in total synthesis of normalindine.

Treatment of **68** and **69** in DCB at 150 °C in the presence of 1,5-diazabicyclo[4.3.0]non-5ene, an application of Weinreb's procedure, resulted in a retro-Michael reaction. In a similar fashion, the 3:1 mixture of the (*Z*)-isomers **70** and **71** afforded the adduct (**74**) in 40% yield. No adducts arising from the

minor diastereomers **69** and **71** were obtained. Conversion of three adducts **72**, **73**, and **74** into pyridine derivatives was then investigated (Scheme 1.11).

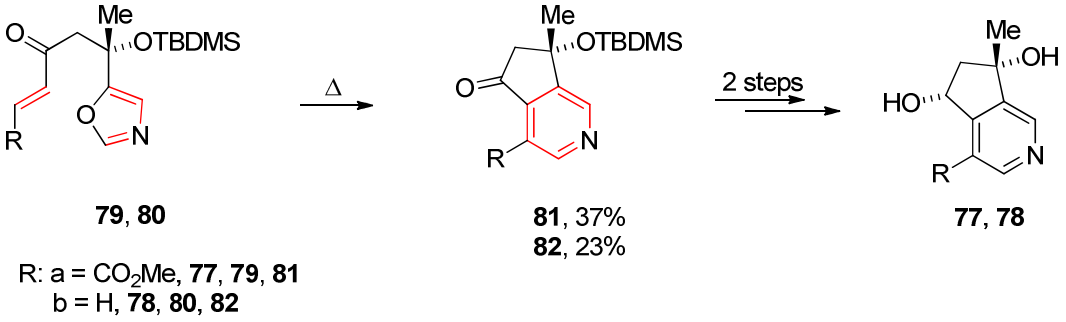


Scheme 1.11 Final steps in total synthesis of normalindine.

On treatment with 1,5-diazabicyclo[4.3.0]non-5ene in refluxing toluene for 10 h, the adduct **72** underwent a retro-Diels–Alder reaction and no product possessing the desired skeleton was obtained. However, the C(2)-O bond cleveage of **72** was found to be facile upon exposure to AcOH at room temperature for 1 h, affording the diol (**75**) in 77% yield with concomitant addition of water to the imino group. The desired ester (**76**) was eventually obtained in 18% yield, accompanied by recovered **75** (62%). Under these conditions, the adduct **74** gave results analogous to those obtained from **72**. Alkaline hydrolysis of **76** with LiOH followed by the modified Curtius rearrangement[34] using diphenyl phosphoroazide furnished the carbamate compound, which finally was converted to the target compound **63** by treatment with TFA and subsequent reductive deamination of the resulting arylamine with butyl nitrite in DMF.

1.6 Effect Of Copper (II) trifluoromethanesulfonate On The Intramolecular Diels–Alder Reaction Of Oxazole-Olefins

Ohba and co-workers[35] reported total syntheses of the monoterpene alkaloids (–)-plectrodorine (**77**) and (+)-oxerine (**78**) (Scheme 1.12), possessing a cyclopenta[*c*]-pyridine ring system. The yields of the IMDA reactions of the oxazole-olefins **79** and **80**, exploited as a key step of the synthesis, were significantly low.



79, **80**

R: a = CO_2Me, **77**, **79**, **81**
b = H, **78**, **80**, **82**

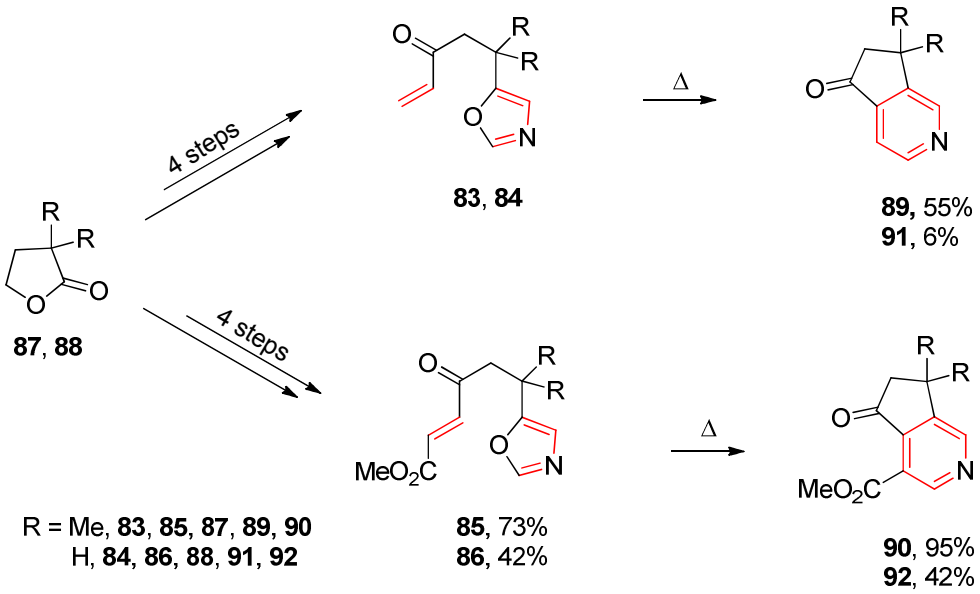
81, 37%
82, 23%

77, **78**

Scheme 1.12 Total synthesis of monoterpene alkaloids (–)-plectrodorine and (+)-oxerine.

This led the group towards investigation of the effect of Lewis acids on the corresponding cycloaddition of the dimethyl substituted derivatives (**83**) and (**85**) (Scheme 1.13).[30] The requisite oxazole-olefins **83**, (**84**), **85** and (**86**) were prepared from lactones (**87**) and (**88**) according to their previous procedure for **79** and **80**.[35] With four model oxazole-olefins **83–86** in hand, Ohba and co-workers firstly examined the IMDA reaction of **83** in detail. Heating a 0.05 M solution of **83** in DCB at 150 °C under argon for 24 h provided the cyclopenta[*c*]-pyridine (**89**); the yield however was only 21%. Although Weinreb used 1,5-diazabicyclo[4.3.0]non-5ene successfully in intramolecular oxazole-olefin Diels-Alder reactions,[28] no formation of **89** was observed in the presence of the amidine. As the first example of Lewis acid catalysis of oxazole-olefin cycloadditions, Levin recorded the results of investigation on the effect of europium salts.[36] In the case of **83**, however, addition of $Eu(fod)_3$ failed to

improve the yield of **89**. Fortunately, several metal trifluoromethanesulfonates, such as Yb (III), Sc (III) or Cu (II) proved to be effective promoters of the cycloaddition of **83**. The best result was obtained by heating **83** in DCB in the presence of 2 mol% of copper (II) trifluoromethanesulfonate at 180 °C for 1 h; under these conditions **89** was produced in 55% yield.



Scheme 1.13 Lewis acid effect on IMDA oxazole olefin cycloaddition reactions.

A dramatic rate enhancement was observed for the cycloaddition of **85** possessing an ester group on the terminal olefin when a catalytic amount of $Cu(OTf)_2$ was employed. In the absence of the catalyst, (**90**) was obtained in only 15% yield together with unaltered **85** (73%) after 24 h at 150 °C, whereas smooth cycloaddition occurred in the presence of 2 mol% of $Cu(OTf)_2$ giving **90** in 95% yield after 30 min. Addition of $Eu(OTf)_3$ again failed to effect any improvement. Under the influence of 10 mol% of $Cu(OTf)_2$, the above reaction proceeded even at higher temperature, reflux in DCB.

Finally, the Ohba group focused their attention on the IMDA reaction of the unsubstituted substrates **84** and **86**. As compared with the dimethyl substituted compounds, the cycloaddition of **84** and **86** turned out to be apparently slow and less effective. Thus, heating a 0.05 M solution of **84** in *o*-DCB at 180 °C for

24 h produced (**91**) in a poor (6%) yield along with unaltered **84** (30%). Even in the presence of copper (II) trifluoromethanesulfonate (10 mol%), the yield of **91** remained low after 8 h (24%). Although this cycloaddition was somewhat promoted by the introduction of the ester group on the terminal olefin of **86**, the yield of (**92**) was moderate (42%).

Ohba and co-workers clarified that the IMDA reaction of **83** and **85** are considerably accelerated in the presence of copper (II) trifluoromethanesulfonate to provide cycloaddition products in moderate to excellent yields. The large enhancement, namely a "*gem*-dimethyl effect" or Thorpe–Ingold effect[37], observed for the dimethyl substituted substrates **83** and **85** may be explained in terms of the "reactive rotamer effect" described by Jung.[38]

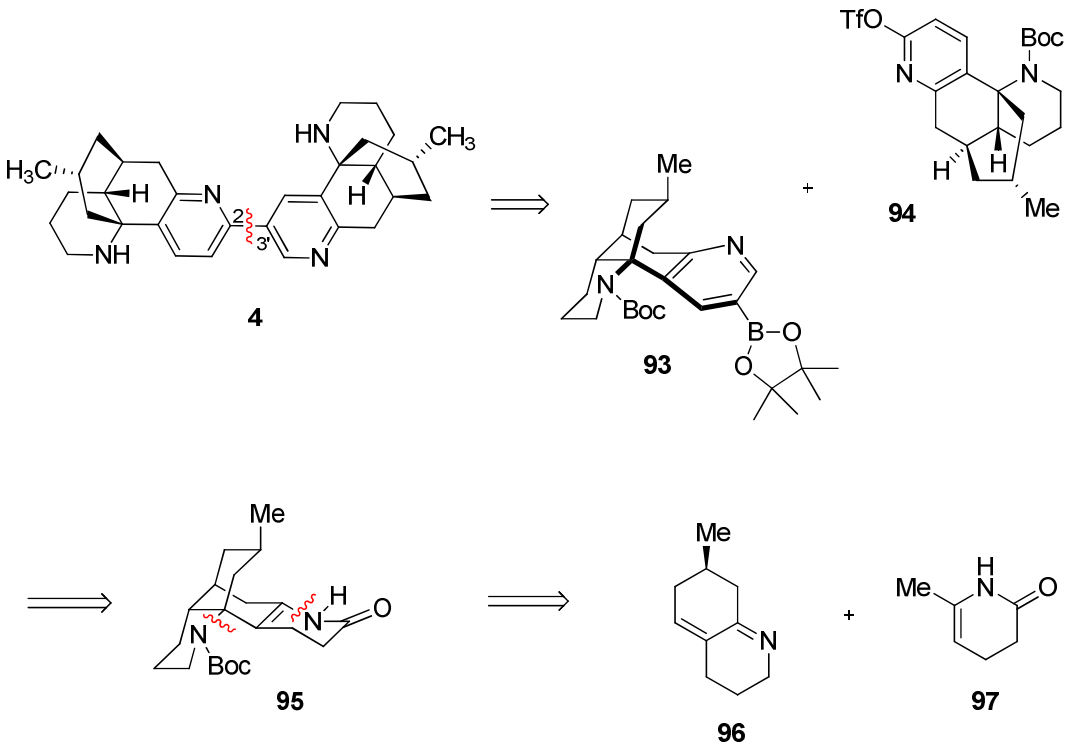
1.7 Total Syntheses Of Complanadine A

In 2010, two independent research groups simultaneously reported the first total syntheses of complanadine A. Fisher and Sarpong[39] and Siegel and co-workers[40] employed entirely different approaches, which are discussed separately below.

1.7.1 Fisher and Sarpong's Total Synthesis of Complanidne A

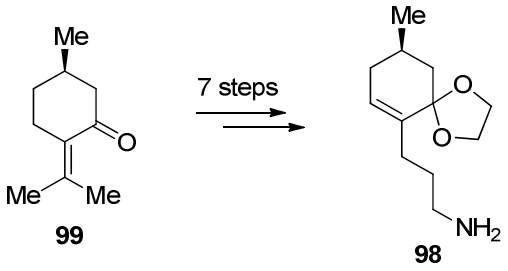
Fisher and Sarpong's approach employed an iridium-catalysed pyridine C-H functionalisation[41] as a key step. The authors envisaged that a powerful simplification of the synthesis would entail formation of (**93**) and (**94**) from an intermediate such enamide (**95**). The enamide was in turn envisaged to arise from acid-promoted formal cycloaddition of (**96**) and (**97**) following the

precedent of Schumann for the synthesis of racemic *N*-desmethyl-α-obscurine (Scheme 1.14).[42]



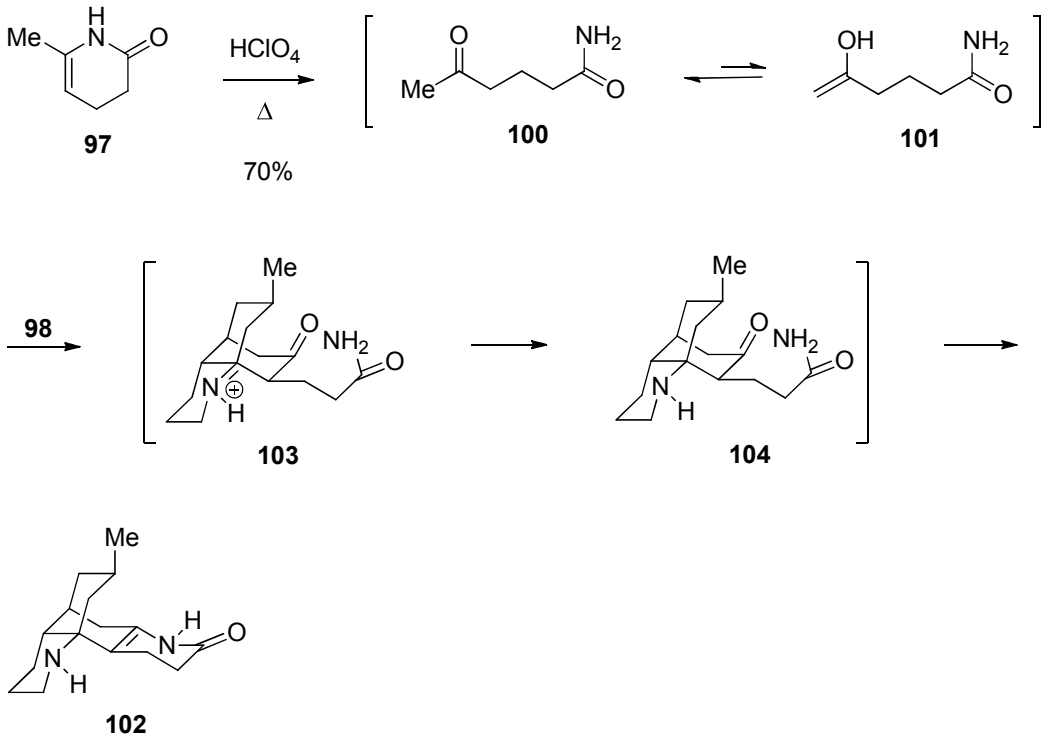
Scheme 1.14 Retrosynthetic analysis of Complanadine A by Fisher and Sarpong.

They commenced the synthesis with the preparation of the ketal (**98**) from (+)-pulegone (**99**) using literature procedures over 7 steps (Scheme 1.15).



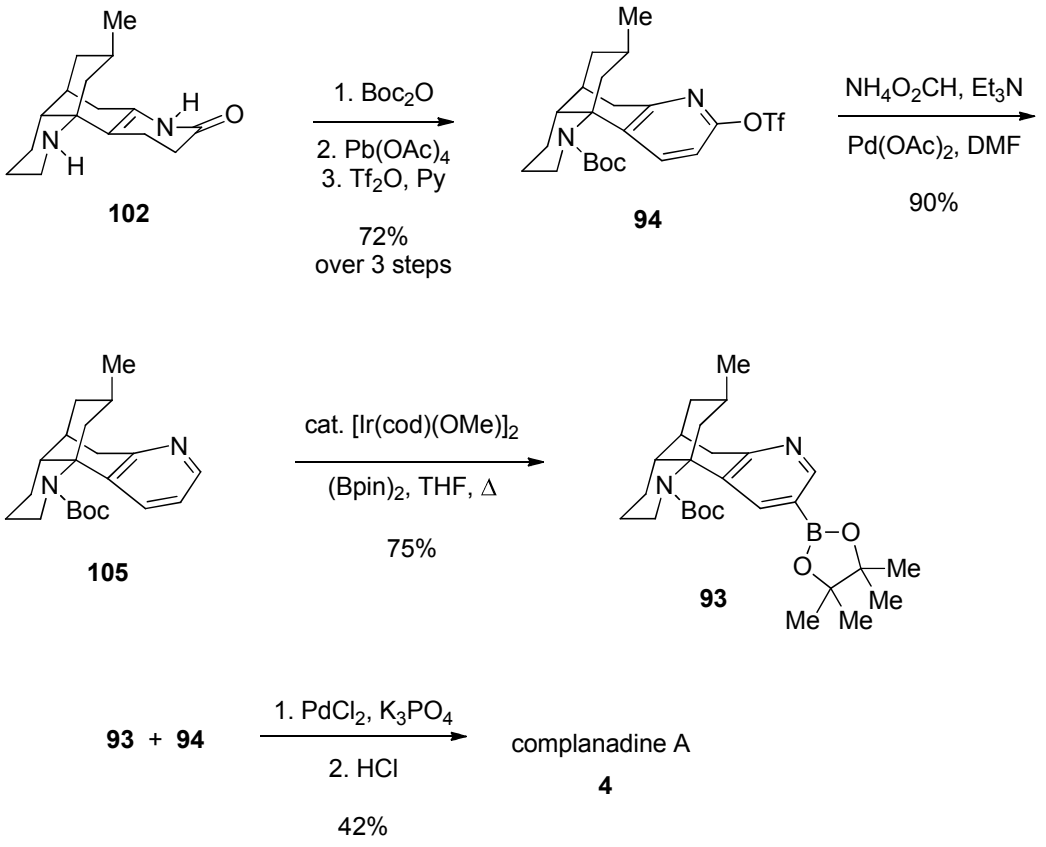
Scheme 1.15 Preparation of the ketal 98.

Enamide **97** was hydrolysed with perchloric acid to generate the reactive enol tautomer (**101**) (Scheme 1.16). The addition of the ketal **98**, which is deprotected *in situ*, initiated the *N*-desmethyl-α-obscurine cascade (**102**) proceeding by a series of cyclisations (*via* **103** and **104**).



Scheme 1.16 The *N*-desmethyl-α-obscurine cascade.

Boc protection of **102** was followed by oxidation to the pyridone with lead tetraacetate. Subsequent triflation then furnished derivative **64**, which was converted to Boc-protected lycodine (**105**) after removal of the triflate using Pd-catalysed reducing conditions (Scheme 1.17).



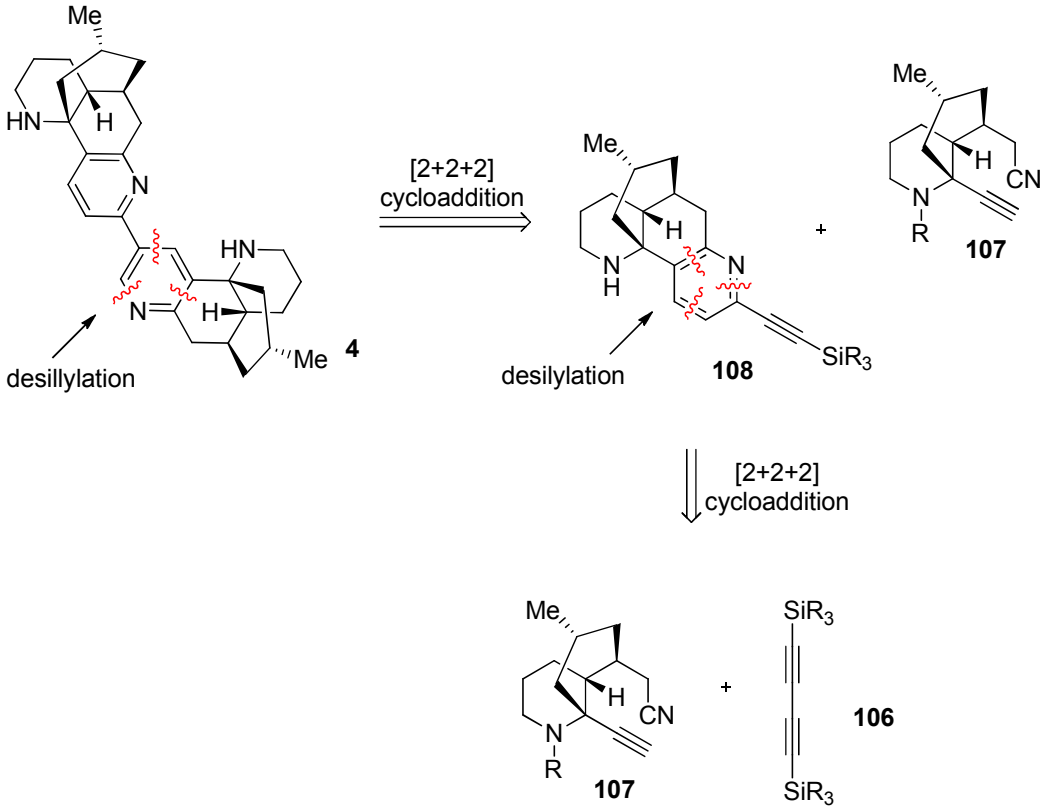
Scheme 1.17 Suzuki cross-coupling of the boronic ester and the triflate.

The conversion of **94** to **105** was achieved in a single step. The Ir(I)-catalysed borylation chemistry yielded the boronic ester **93**. Finally Suzuki cross-coupling[43-45] of boronic ester **93** and triflate **94** followed by cleavage for the Boc protecting group the complanadine A **4** in 42% yield.

1.7.2 Siegel's total synthesis of the Complananidne A

Siegel and co-workers took a markedly different approach to the synthesis of complanadine A. They envisaged the pseudosymmetry of the molecule could be accessed by implementation of a metal mediated [2+2+2] + [2+2+2]

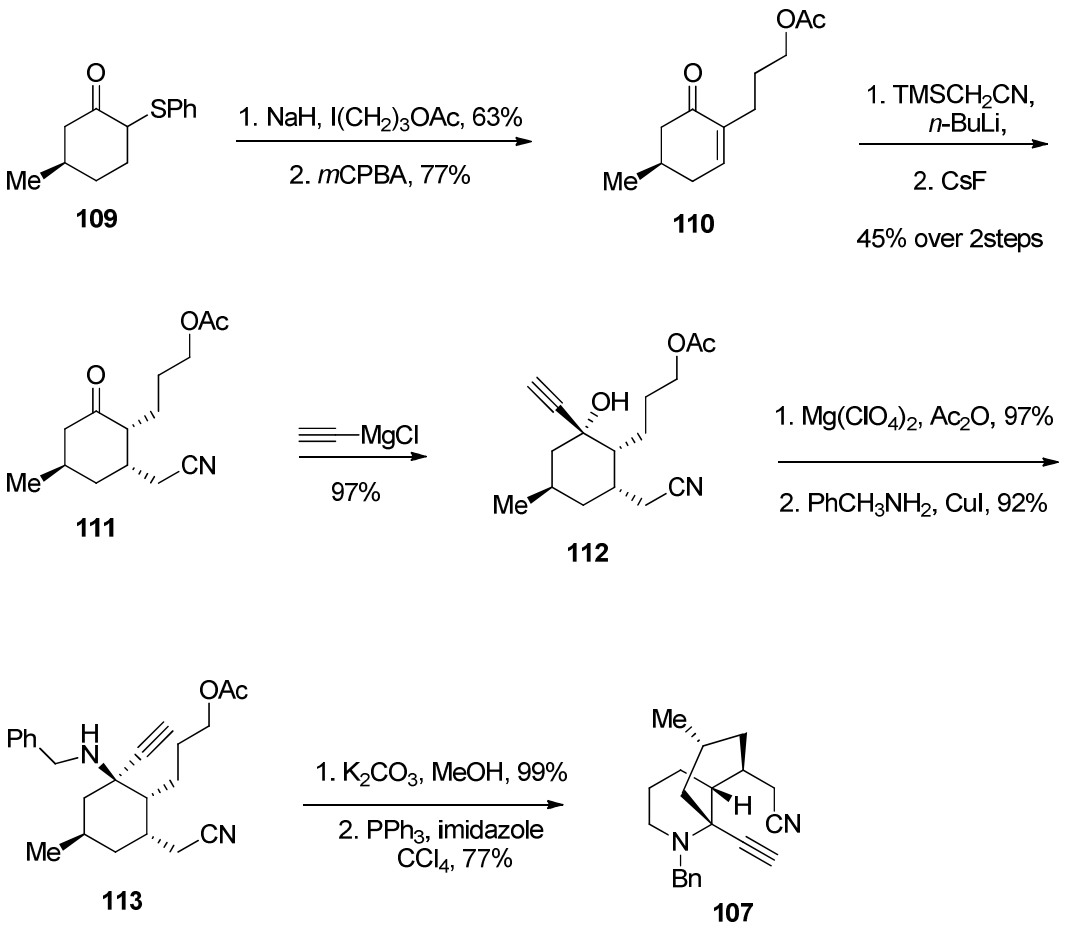
sequence using a substituted diyne (**106**) and two equivalents of the corresponding alkyne-nitrile (**107**) (Scheme 1.18).



Scheme 1.18 Synthetic disconnections of Complanadine A by Siegel.

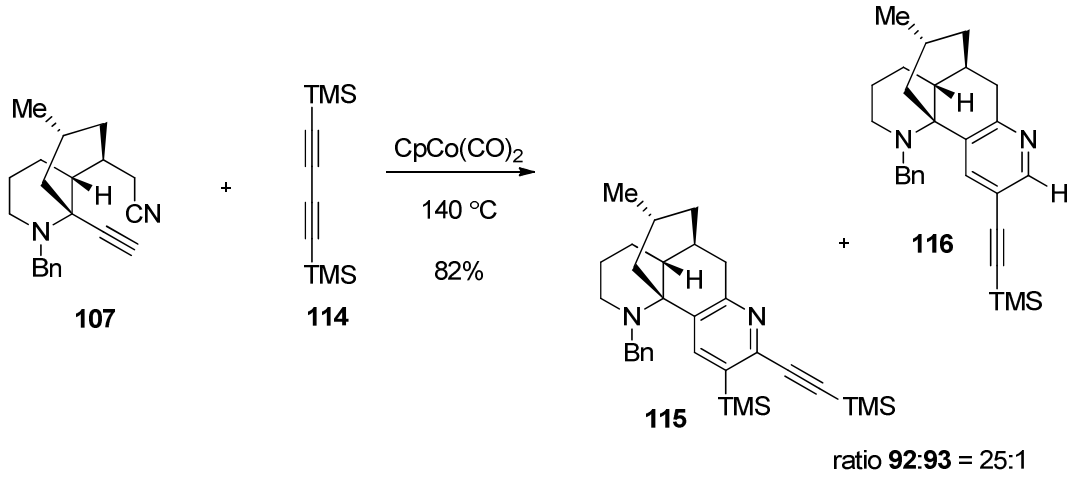
They began the synthesis of the required alkene-nitrile **107** from the enolate of thioether (**109**), reacting with 3-iodopropyl acetate (Scheme 1.19). Further oxidation with *m*-CPBA and a mild sulfoxide elimination derived enone (**110**). Treatment of the enone **110** with the anion of trimethylsilyl acetonitrile produced the Michael adduct as a mixture of diastereomers, but after desilylation with cerium fluoride, the desired diastereomer (**111**) was easily separated. Diastereoselective delivery of ethynylmagnesium chloride into the ketone cleanly provided the corresponding propargyl alcohol (**112**) as a single isomer. Activation of the alcohol **112** as the corresponding acetate provided a precursor for a copper mediated amination reaction. Further reaction of **112** with benzylamine and substoichiometric amount of CuCl delivered the propargyl

amine (**113**) in a high yield with complete diastereoselectivity. Transformation of the secondary amine **113** into the desired alkyne-nitrile **107** was accomplished over 2 steps (Scheme 1.19).



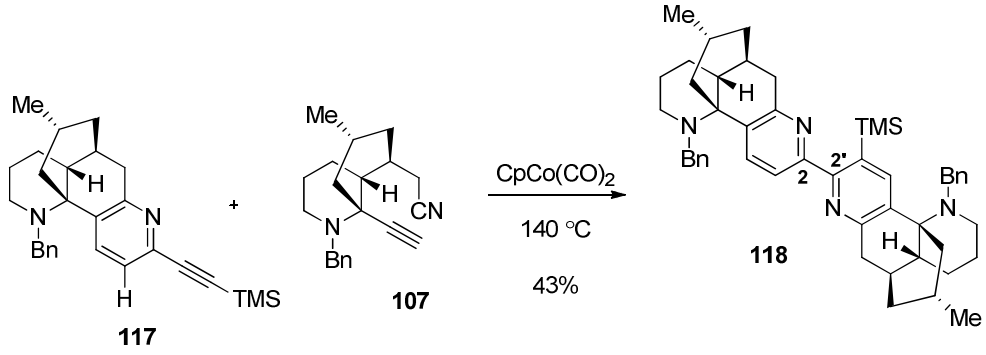
Scheme 1.19 Synthesis of the alkyne-nitrile 107.

The first [2+ 2+2] cycloaddition of the alkyne-nitrile **107** and bis(trimethylsilyl)-butadiyne (**114**) proceeded smoothly, heating the mixture of the two in the presence of $CpCo(CO)_2$, deriving the desired cyclisation product (**115**) as the main regioisomer (Scheme 1.20). However, after a series of trials and a variety of conditions, pyridyl-alkyne **115** did not undergo the second [2+2+2] cycloaddition with the alkyne-nitrile **107**.



Scheme 1.20 [2+2+2] cycloaddition of the alkyne-nitrile and bis(trimethylsilyl)butadiyne.

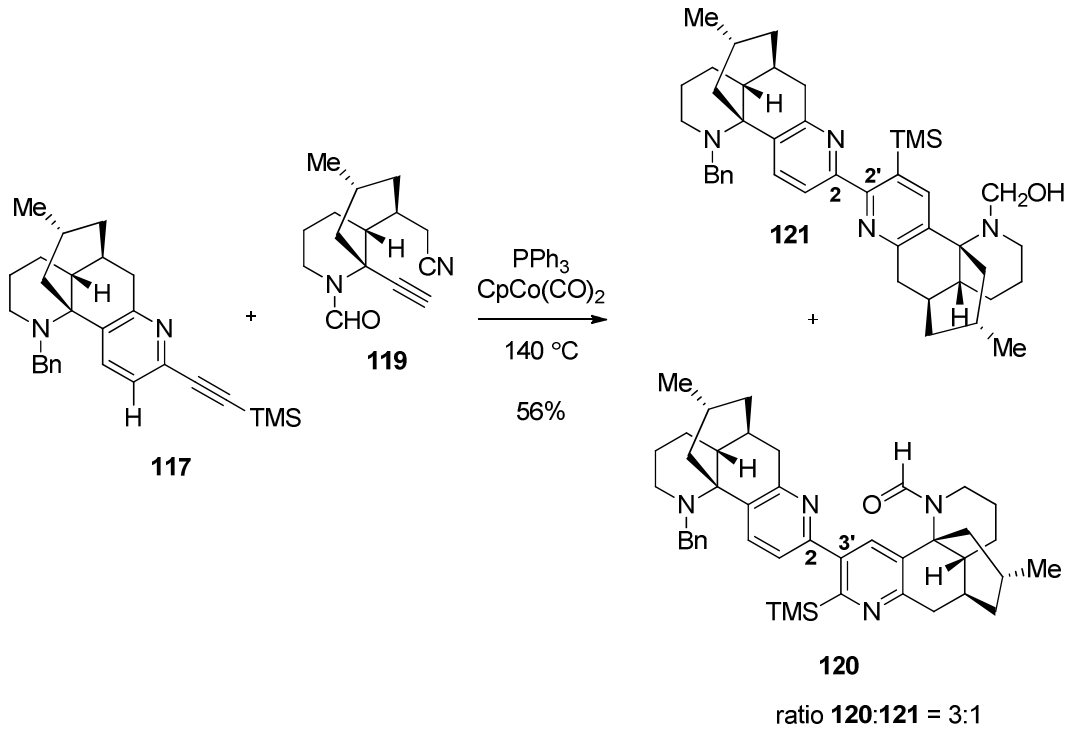
Removing both TMS groups produced a derivative that was too reactive and which led to decomposition upon attempted [2+2+2] cyclisation. The monosilylated alkyne (**117**) in a reaction with alkyne-nitrile **107** under the same conditions resulted a single compound, the symmetric 2,2'-bipyridyl (**118**) rather than the desired 2,3'-bipyridyl isomer (Scheme 1.21).



Scheme 1.21 Synthesis of the 2,2'-bipyridinyl 118.

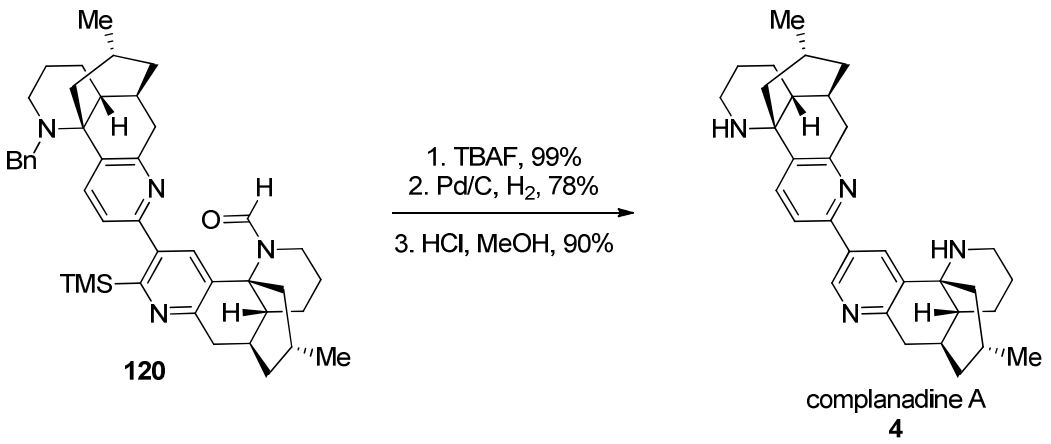
The authors state that after '*significant experimentations*' they found that using the formyl protecting group on the alkyne-nitrile (**119**) and in the presence of the PPh_3, they achieved a remarkable switch in regioselectivity and accessed the desired compound (**120**) as the major isomer (1:3, **120**/**121**) (Scheme 1.22).

The authors state that the ability of triphenylphosphine to alter the regioselectivity '*warrants further study*'.



Scheme 1.22 Second [2+2+2] annulation of the formyl protected alkyne-nitrile 119 and the pyridyl-alkyne 117.

Further fluoride mediated removal of the TMS group, debenzylation by hydrogenolysis and subsequent deformylation using hot acidic methanol solution generated (+)-complanadine A **4** (Scheme 1.23).



Scheme 1.23 Final steps to complanadine A.

Chapter 2

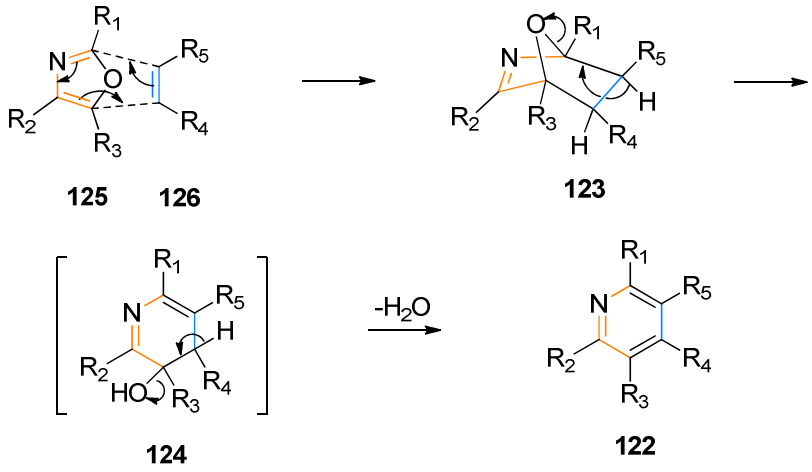
Results and discussion 1

2. RESULTS AND DISCUSSION I

2.1 Retrosynthetic Analysis of Complanadine A

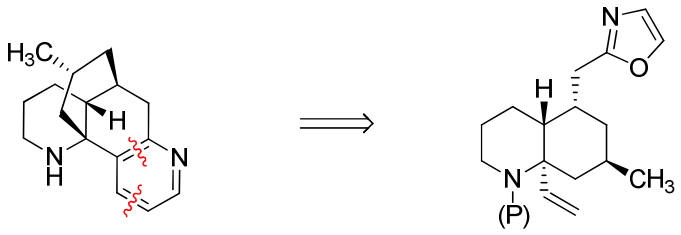
The first total synthesis of racemic lycodine **9** was reported by Heathcock[46,47] based on an intramolecular Mannich condensation strategy, in which sequential construction of the three aliphatic rings preceded the final major event, formation of the pyridine from a 1,5-dicarbonyl. A different approach using a pyridine based starting material was published in 2010 by Tsukano and Hirama.[48] Their stereoselective total synthesis of lycodine proceeded *via* use of Diels–Alder and intramolecular Mizoroki–Heck reactions, starting with methyl 3-hydroxy-2-pyridinecarboxylate.

The key reaction in our proposed synthesis is an intramolecular Kondrat'eva oxazole–olefin hetero-Diels–Alder reaction.[26,27,49] This reaction furnishes substituted pyridines (**122**) *via* ring opening of adduct (**123**) and loss of water from (**124**) (Scheme 2.1).



Scheme 2.1 Intramolecular Kondrat'eva oxazole–olefin hetero-Diels–Alder reaction mechanism.

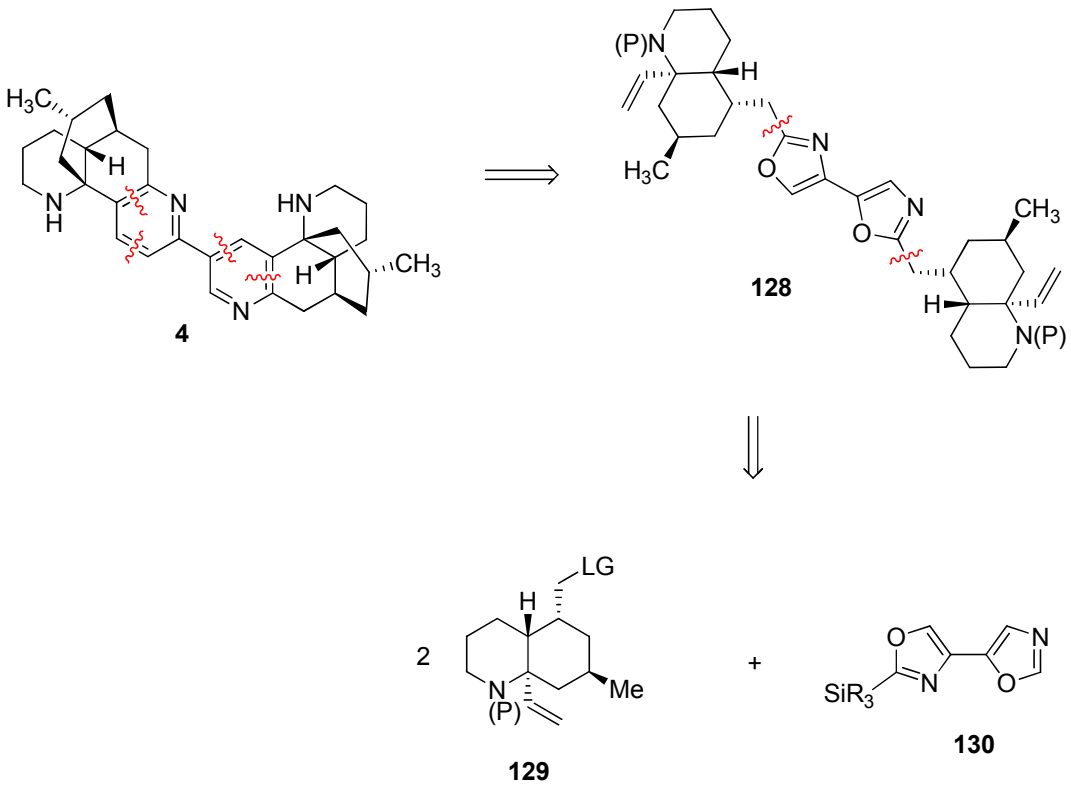
In the context of lycopodium alkaloids this is a powerfully simplifying disconnection, as **9** may thus be accessed from a *trans*-fused azabicycle (**127**) to which is appended an oxazole and a vinyl group (Scheme 2.2).



9 **127**

Scheme 2.2 Kondrat'eva reaction disconnection of lycodine.

In the heterodimeric series, complanadine A **4** is proposed to be accessed from a precursor (**128**) containing a central bis(oxazole) core linked to two equivalent bicyclic fragments (**129**). This in turn is constructed by sequential alkylation of the mono-protected bis(oxazole) (**130**) core (Scheme 2.3).

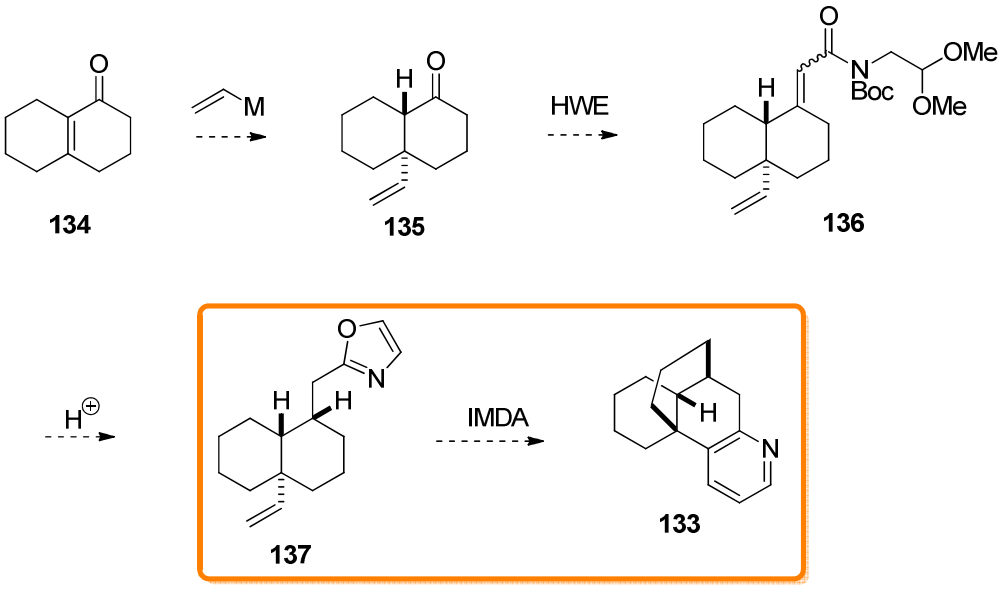


Scheme 2.3 Initial disconnection of complanadine A by Kondrat'eva reaction.

The desired 2,3'-bipyridyl linkage derives from the connectivity in the bis(oxazole) **130** core. The use of the Kondrat'eva pyridine formation in total synthesis is well-precedented; in the intramolecular mode, a four-atom linker between diene and dienophile has been determined to be optimal[26-29,33,50] as in the case here. In **127** both diene and dienophile are required to be axial for pyridine formation – this corresponds to the *trans*-decalin *chair-chair* conformation (**131**) (Scheme 2.4).

Scheme 2.4 Decalin conformers.

The use of this key transformation at such a late stage in the forward synthesis is potentially a high-risk strategy. Accordingly, we decided to mitigate this risk by carrying out a model study. To prove the viability of the intramolecular hetero-Diels–Alder cyclisation, we aimed to prepare a pyridine precursor in which the diene and dienophile would have the same spatial arrangement and electronic properties as in the real system. However, by omitting functionality which was not anticipated to affect directly the cyclisation, we would be able to access the pyridine precursor more rapidly. Accordingy, we aimed to retain the *trans*-decalin backbone, but to remove the endocyclic nitrogen and the methyl group. We also did not consider absolute stereochemistry, but targeted a racemate. Model substrate (**133**) would be quickly accessible by means of Michael addition to α,β-unsaturated ketone (**134**) providing vinyl derivative (**135**); further functional group transformations would give oxazole (**137**), which when subjected to IMDA conditions would furnish the model pyridine **133** (Scheme 2.5). The reaction highlighted in orange indicates our key intramolecular Kondrat'eva oxazole–olefin hetero-Diels–Alder reaction.

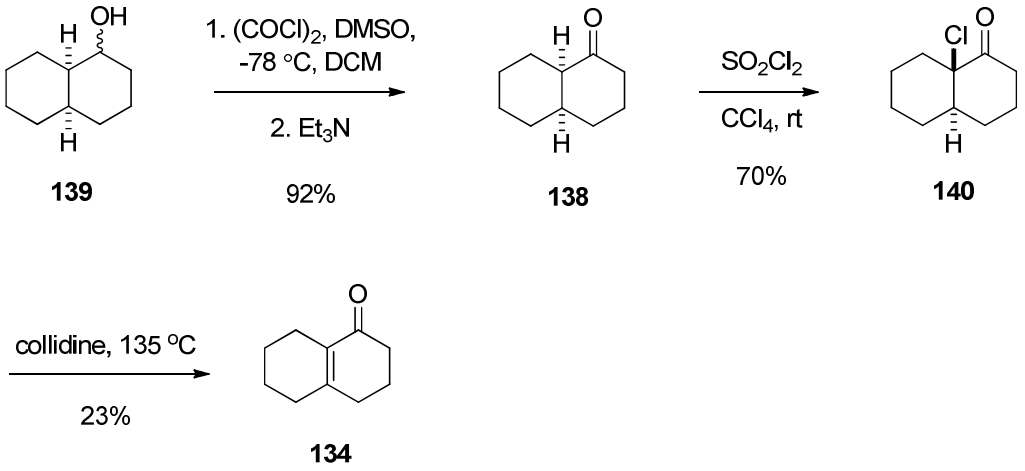


Scheme 2.5 Proposed 1st generation approach.

2.2 Synthetic Results for Model System

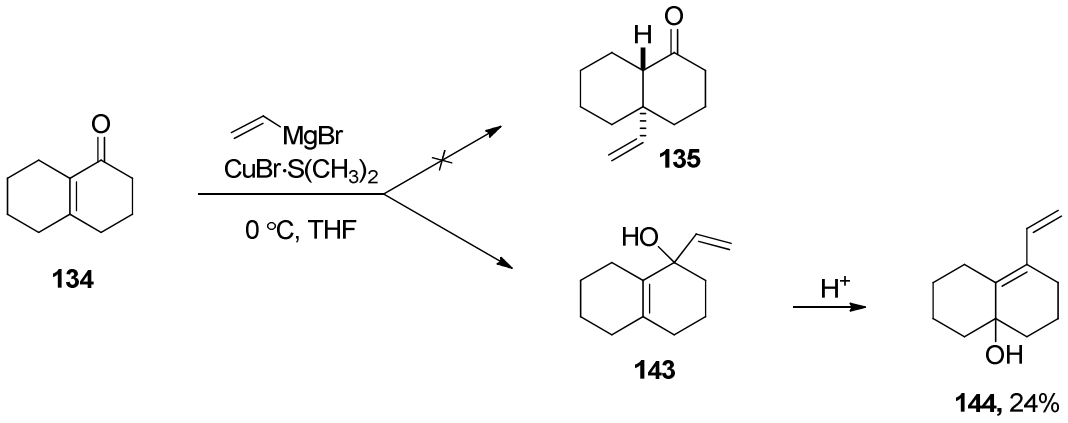
2.2.1 Enone Functionalisation Approaches

To access ketone (**138**) from commercially available *cis*-decahydronaphthalen-1-ol (**139**), the Swern oxidation[51] was used, providing the product in high yield (Scheme 2.6). Halogenation of ketone **138** with sulfuryl chloride afforded desired product (**140**). Further thermal dehydrohalogenation of the chloroketone **140** with collidine at 135 °C furnished desired ketone **134** in 23% yield.



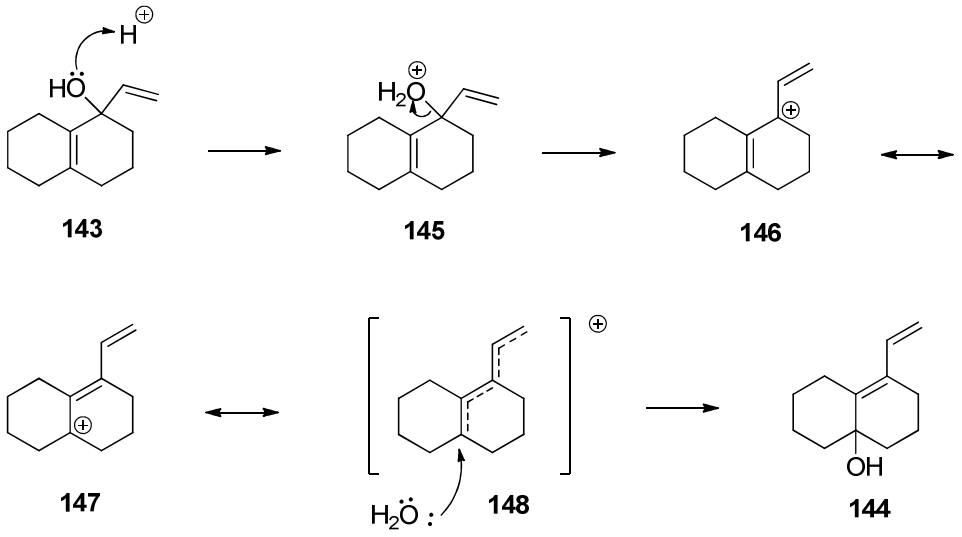
Scheme 2.6 Synthesis of α,β-unsaturated ketone 110.

A test reaction of conjugate addition to a structurally similar 2-cyclohexen-1-one (**141**) suggested use of 2 equiv. of vinylmagnesium bromide and 0.5 equiv. of Cu (I) salt to give the highest percentage of desired Michael addition product. Using these conditions, the reaction of ketone **134** with vinylmagnesium bromide in the presence of copper bromide–dimethyl sulfide complex proceeded *via* 1,2 addition, providing the alcohol (**143**) as the sole product (Scheme 2.7).



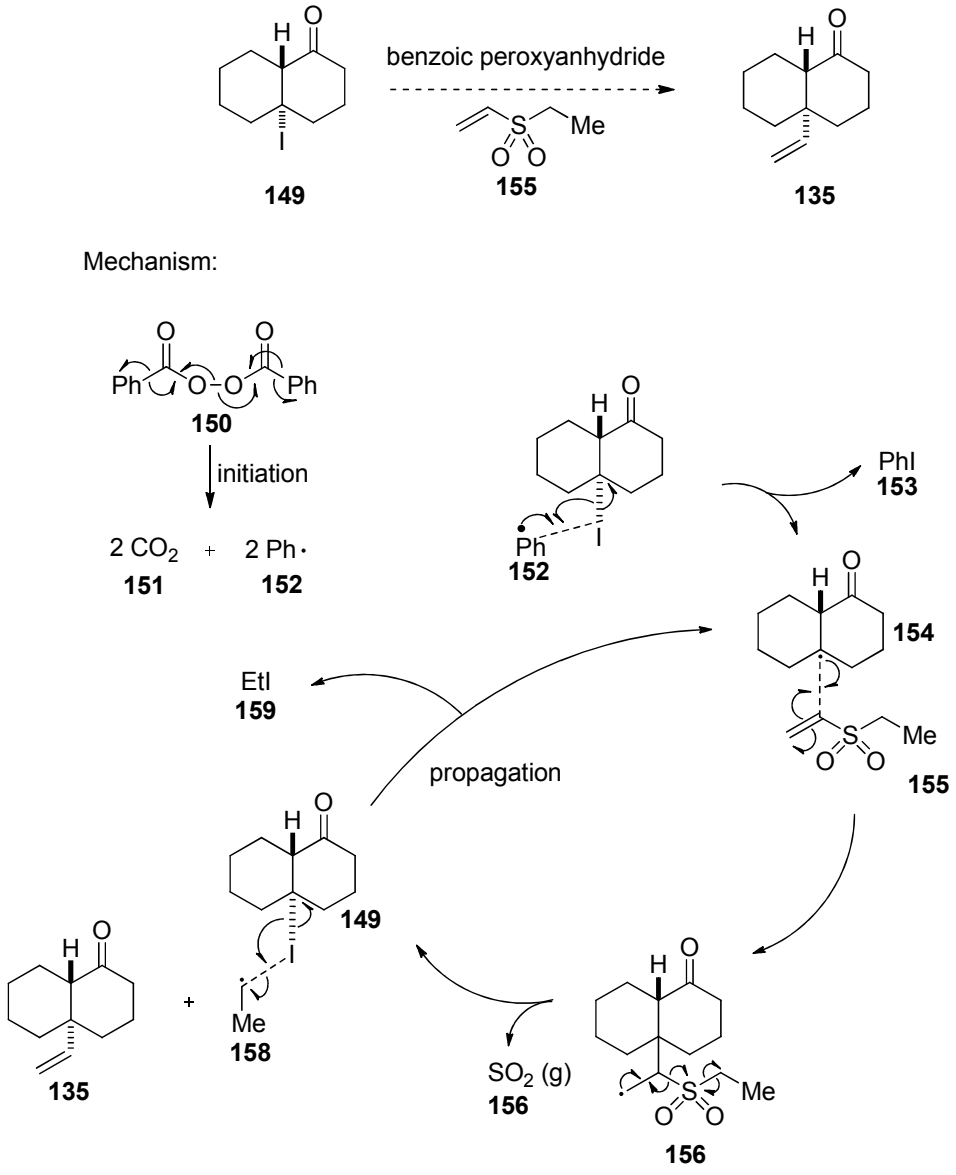
Scheme 2.7 Michael addition of vinylmagnesium to α,β-unsaturated ketone 110.

Acid catalysed isomerisation of vinyl alcohol **143** occurred during column purification, giving the (**144**) in 24% yield. A possible isomerisation mechanism is proposed below (Scheme 2.8). It was interesting to observe differences in the spectra of the crude and the product after column. Characteristic vinyl group proton resonances were observed in both cases. However, the isomerised compound has a conjugated diene system, which results in the vinyl CH_2=C*H*-proton signal shifting downfield by approximately 1 ppm.



Scheme 2.8 Possible isomerisation mechanism of 143.

The unsuccessful synthesis of ketone **135** *via* cuprate addition to the α,β-unsaturated system led us to considerer of a radical vinylation, using methodology developed by Zard[52], which required use of β-iodoketone (**149**) and ethylsulfonylethene (**155**) as vinyl radical source (Scheme 2.9). This was also unsuccessful.

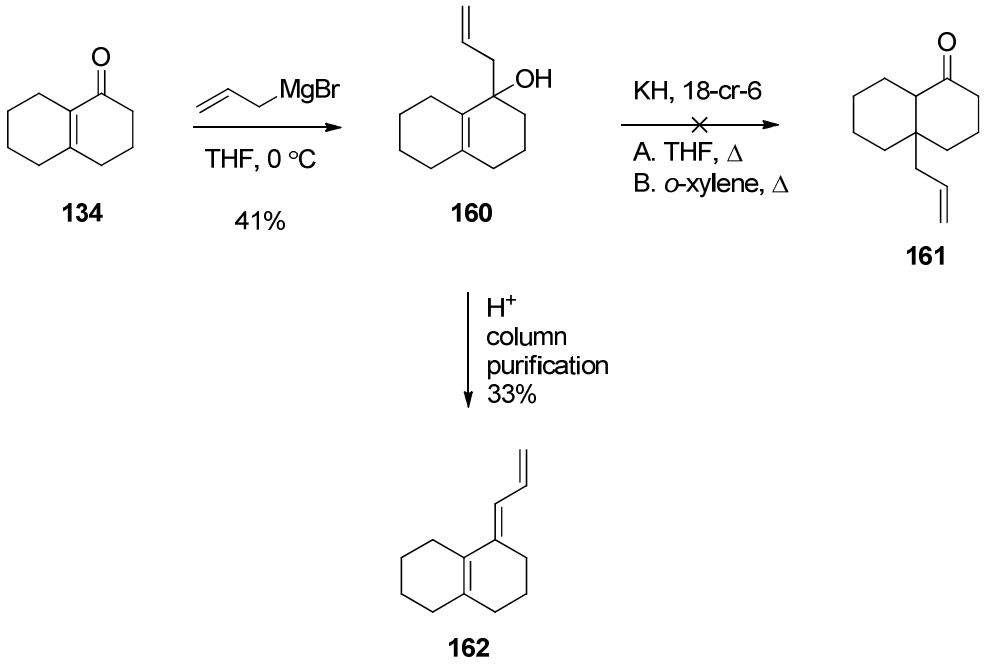


Scheme 2.9 Possible radical vinylation of β-iodoketone 149 by Zard and the mechanism of the reaction.

We next considered other two-step procedures to form **135**, by means of other enone β-functionalisation protocols. Attempts to synthesise ketone **149** using methodology reported by Marx[53] wherein tetraalkyl ammonium iodides react with enones in trifluoroacetic acid at rt to give β-iodoketones were not successful and only starting material was recovered. A report from Miller and McKean[54] on preparation of β-iodoketones, utilizes low temperature 1,4-addition of trimethylsilyliodide to enones to give the intermediate iodo TMS enol ethers, followed by hydrolysis of these to the β-iodoketones. Unfortunately in our case only starting material was recovered. Attempts accessing the β-bromoketone by bubbling HBr gas through a solution of **134** in DCM were fruitless as well.

After the failure to synthesise the desired vinyl ketone **135**, we examined the addition of allylmagnesium bromide in order to effect a 1,2 addition to the ketone **134**. This would provide allyl alcohol (**160**) which should undergo an oxyanion-Cope rearrangement,[55] so providing (**161**), which possesses the desired quaternary centre (truncation of the side chain would then be explored)

The allylation of **134** gave alcohol **160** in 41% yield (Scheme 2.10). During column purification **150** underwent elimination of water deriving (**162**). Attempts to induce the rearrangement using KH and 18-crown-6 in THF failed. Surprisingly, some form of retro-allylation occurred and ketone **134** was recovered after column purification in 47% yield. Use of *ortho*-xylene as solvent and elevated temperature resulted in the same outcome.

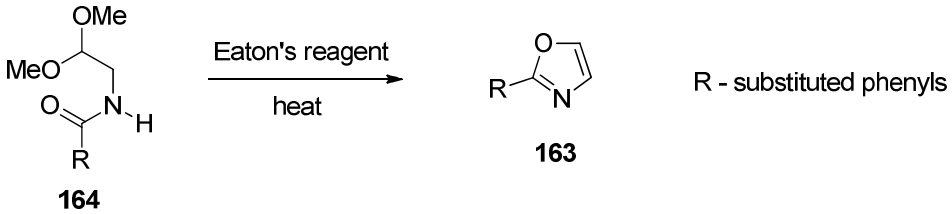


134 **160** **161** **162**

Scheme 2.10 Allylation of ketone 134 and attempted oxyanion-Cope rearrangement.

Concurrently with the reactions described above, approaches towards oxazole **137** were examined.

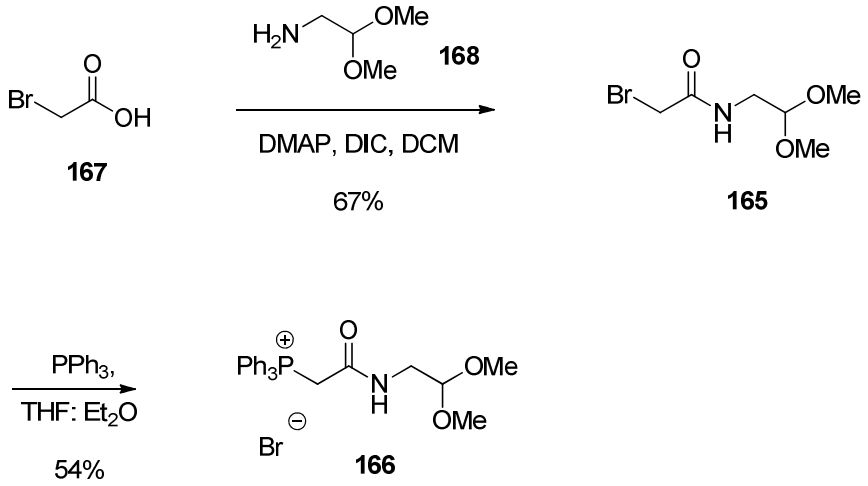
Known methods for synthesis of 2-substituted-4,5-unsubstituted oxazoles are either indirect, low yielding or require expensive reagents. Polniaszek *et al.*[56] have reported the synthesis of 2-substituted oxazoles (**163**) from acetamides (**164**) where bromine was changed to a substituted phenyl group, which is similar to the α-bromo derivative (**165**) required for our purposes. Cyclization using Eaton's reagent[57] (phosphorus pentoxide, 7.7 wt.% solution in methanesulfonic acid) afforded oxazoles in moderate yield (Scheme 2.11).



164 **163**

Scheme 2.11 Polniaszek's synthesis of 2-substituted oxazoles.

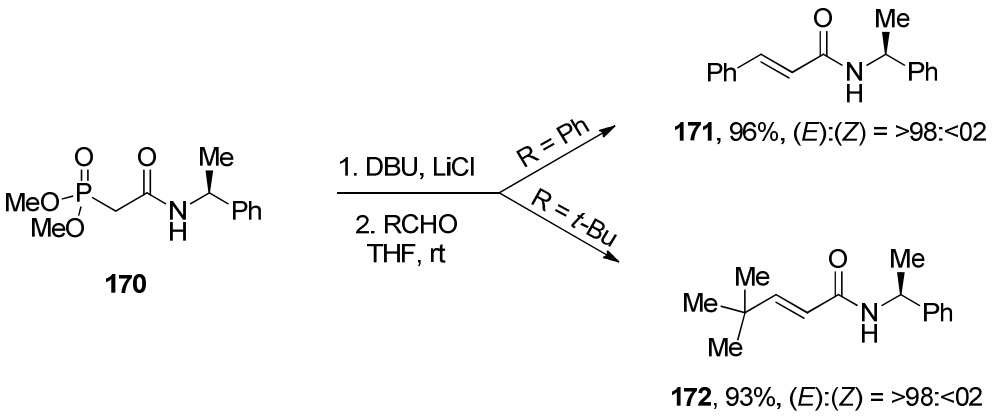
In order to access **137**, acetamide **136** was required. This should be accessible by means of an olefination of the ketone **135** with the phosphorus ylide derived from (**166**). Synthesis of triphenylphosphonium bromide **166** commenced with reaction of α-bromoacetic acid (**167**) with aminoacetaldehyde dimethyl acetal (**168**) to give 2-bromo-*N*-(2,2-dimethoxyethyl)acetamide **165** in 67% yield (Scheme 2.12).



Scheme 2.12 Synthesis of triphenylphosphonium bromide 166.

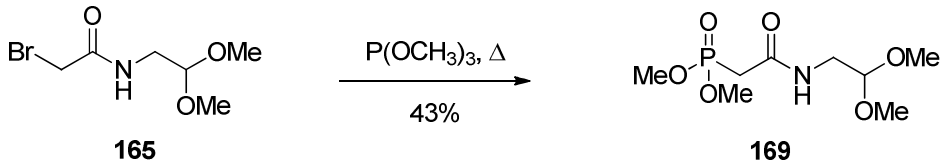
Acetamide **165** was then reacted with triphenylphosphine to form triphenylphosphonium bromide **166** in 54% yield. Attempted Wittig reactions[58] of **166** with cyclohexanone as a test reaction using different bases were not satisfactory. Only traces of the desired olefination product were observed by ^{1}H-NMR. Accordingly, the Horner–Wadsworth–Emmons reaction[59,60] using phosphonoacetamide (**169**) was then explored.

Synthesis of α,β-unsaturated amides from amide-containing phosphonates *via* Horner–Wadsworth–Emmons reactions has been reported by Ordóñez *et al.*[61,62] The viability of the reaction in the presence of a free amide N-H is illustrated (Scheme 2.13). They successfully accomplished syntheses of various α,β-unsaturated amides employing the Masamune–Roush procedure[63].



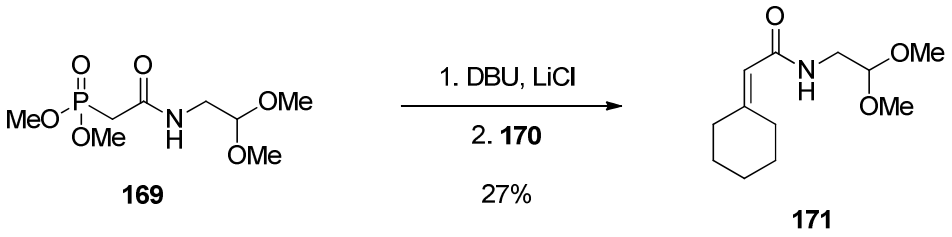
Scheme 2.13 Horner–Wadsworth–Emmons reaction of phosphonamides with free N-H, as reported by Ordóñez.

The required phosphonoacetamide **169** was synthesized by the Michaelis–Arbuzov reaction[64,65] of 2-bromoacetamide **165** with trimethylphosphite under reflux (Scheme 2.14).



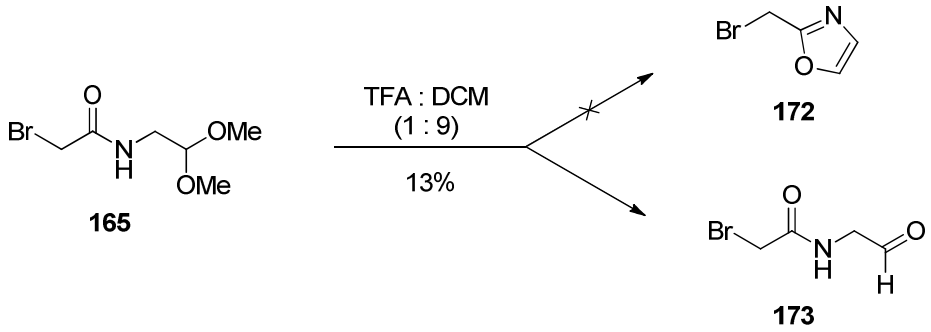
Scheme 2.14 Synthesis of the phosphonoacetamide 169 through Michaelis–Arbuzov reaction.

The viability of the reaction was tested using cyclohexanone (**170**) as substrate, employing the Masamune–Roush modification. The reaction furnished α,β-unsaturated amide product (**171**) in moderate yield (Scheme 2.15).



Scheme 2.15 HWE reaction of the phosphonoacetamide 169 using the Masamune–Roush procedure.

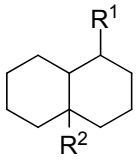
The viability of oxazole formation using Polniaszek's conditions[56] was tested using milder cyclisation conditions - treating acetamide **165** with trifluoroacetic acid (Scheme 2.16). All starting material was consumed within 30 min, but the reaction did not furnish the oxazole ring as desired. Instead, the starting material was hydrolysed to aldehyde (**173**).



Scheme 2.16 Attempted synthesis of 2-(bromomethyl)oxazole 172.

2.2.2 The Baddeley reaction

The unsuccessful attempts at accessing the vinyl ketone **135** by means of conjugate addition or oxyanion-Cope rearrangement led us instead to examine the literature and identify compounds which possessed the required substitution at positions 1 and 4a of the decalin skeleton (**174**) (Figure 2.1):

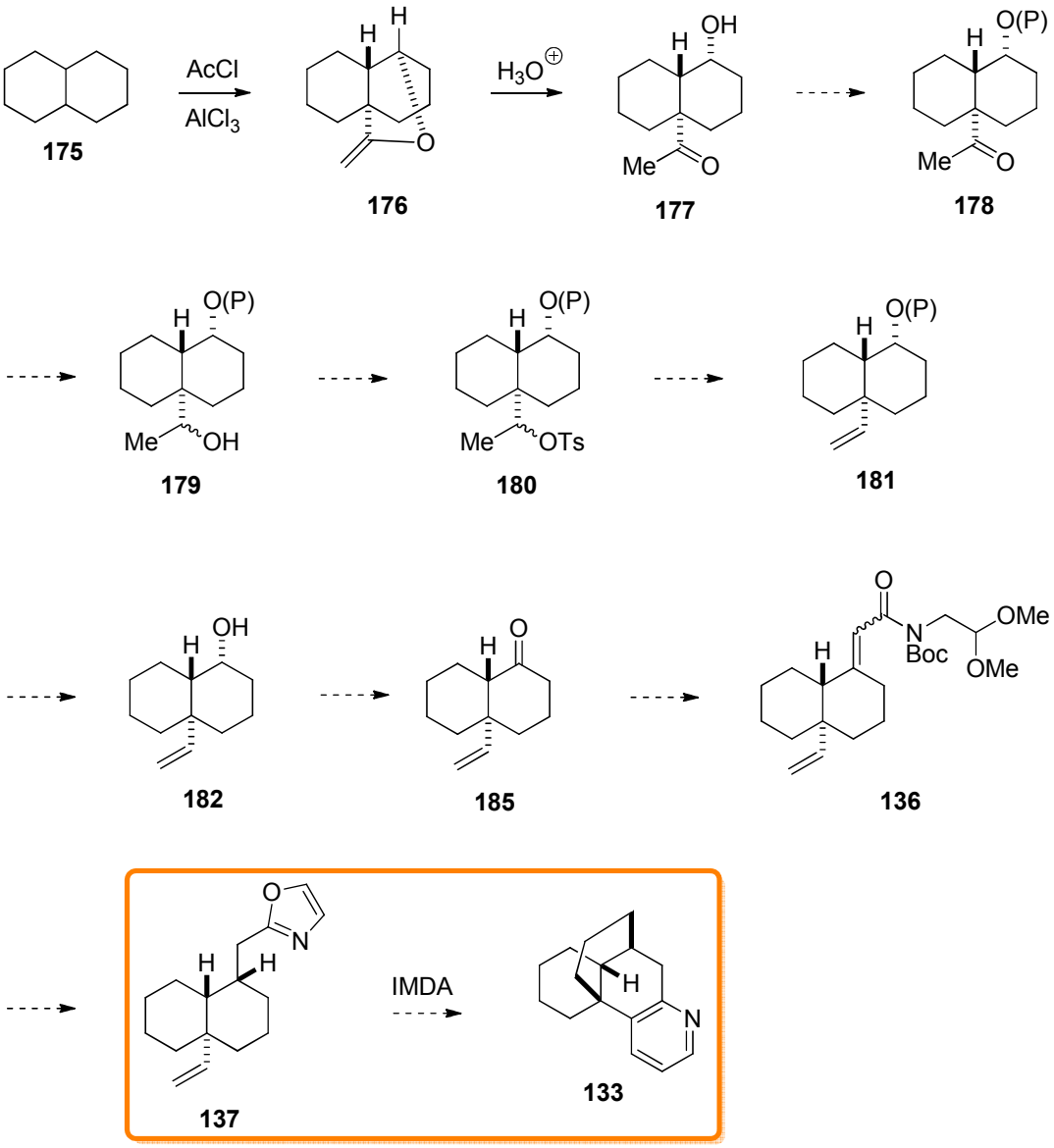


174

Figure 2.1 Desired substitution pattern of the decalin system.

The literature contains reports describing the interaction of decalin (**175**) and the Friedel–Crafts acetylating agent.[66-70] Interaction of decalin and acetyl chloride at a temperature of 10 °C or lower, with an excess of the acid chloride and aluminium chloride furnishes 10β-vinyldecalin 1β,1'-oxide (**176**) in 35-40% yield (see Scheme 2.18). This attracted our interest as it possesses the requisite substituent pattern including a substituent at the ring junction (C4a), which we were not able to access before.

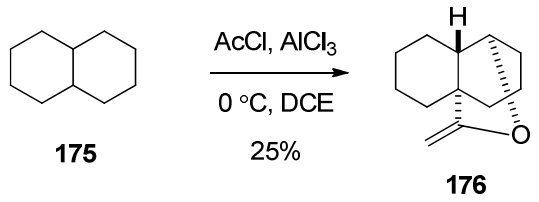
Consideration of the synthetic utility of this "Baddeley reaction" led to the conception of a 2nd generation approach (Scheme 2.17). This approach commences with the use of commercially available and cheap starting materials: decalin, $AlCl_3$ and acetyl chloride, to form the enol ether **176**. Hydrolysis of **176** to access the hydroxy ketone (**177**) is reported. This would be followed by protection of the alcohol to form (**178**) and reduction to derive alcohol (**179**). Transformation of the alcohol to the tosylate (**180**) and a subsequent elimination would give alkene (**181**). Deprotection of vinyl derivative **181** and oxidation of the alcohol (**182**) would lead to formation of the vinyl ketone **135** which then could be used in further steps as per the proposed 1st generation route.



Scheme 2.17 2nd Generation model system *via* decalin acylation.

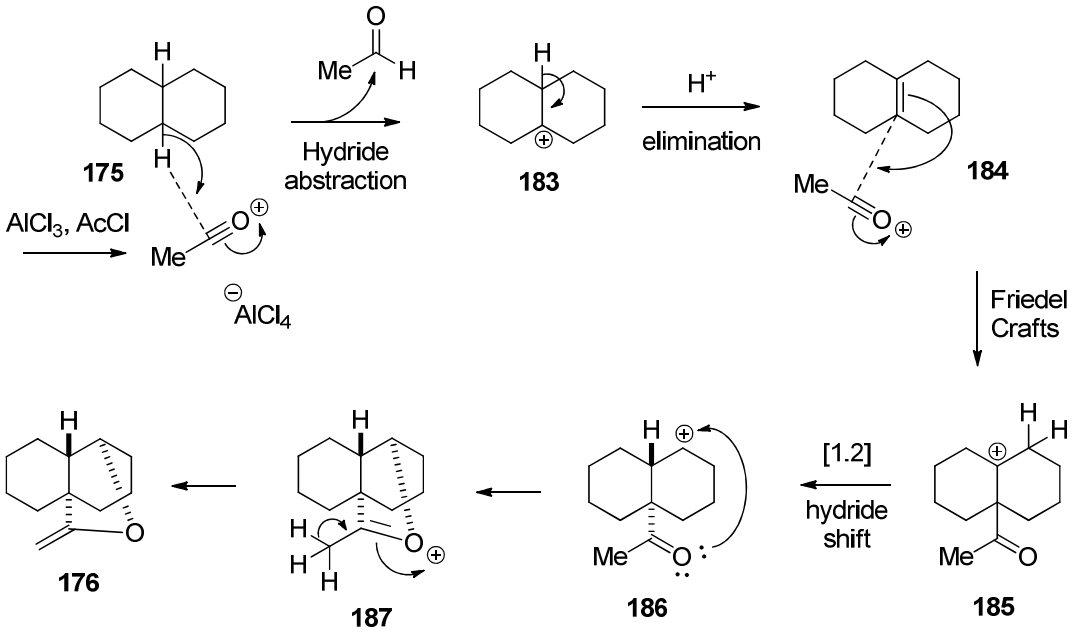
The synthesis of the vinyl ether **176** was repeated using the exact procedure given in the publication. The crude was distilled and additionally purified by refluxing the distillate with lithium aluminium hydride in dry ether to give pure vinyl ether in 25% yield (Scheme 2.18). In the original paper the reaction was performed on 712 g scale; we reproduced it up to 176 g of substrate. At the time of the original publications, all structural assignments were made by means of

IR, elemental analysis and degradation/chemical correlation, as no NMR was available. We were able to confirm the structure using NMR and mass spectrometry data.



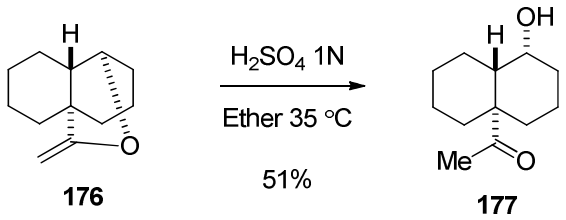
Scheme 2.18 Baddeley acylation of decalin.

The mechanism we propose for this unusual Friedel–Crafts 'aliphatic acylation' is shown in Scheme 2.19. The reaction would begin with formation of an acylium cation, which would then act as a hydride abstractor on decalin **175**, forming tertiary decalin cation (**183**) and liberating acetaldehyde. Through loss of a proton, cation **183** would form $\Delta^{9,10}$-octalin (**184**). Alkene **184** would then react with a second equivalent of acylium cation, forming Friedel–Crafts acylation intermediate (**185**). We next propose a [1,2] hydride shift transforming intermediate **185** from a tertiary to a secondary cation (**186**), which then would cyclise to form oxonium intermediate (**187**). Finally, loss of proton would afford the observed vinyl ether **176**.



Scheme 2.19 Proposed acylation mechanism of decalin.

Acid hydrolysis of the vinyl ether **176** can give two ring opening products. The action of dilute sulfuric acid to **176** in diethyl ether gives the required product **177** in which the C1 hydroxyl and C4a methyl ketone are *cis*.



Scheme 2.20 Synthesis of the hydroxyl-ketone 177, *via* acidic ring opening of 176.

The ring opening reaction in the presence of diethyl ether gave crystalline desired hydroxyl-ketone **176** in 51% yield (Scheme 2.20). The relative stereochemistry of the *cis*- product was determined by X-ray crystallography (Figure 2.2).

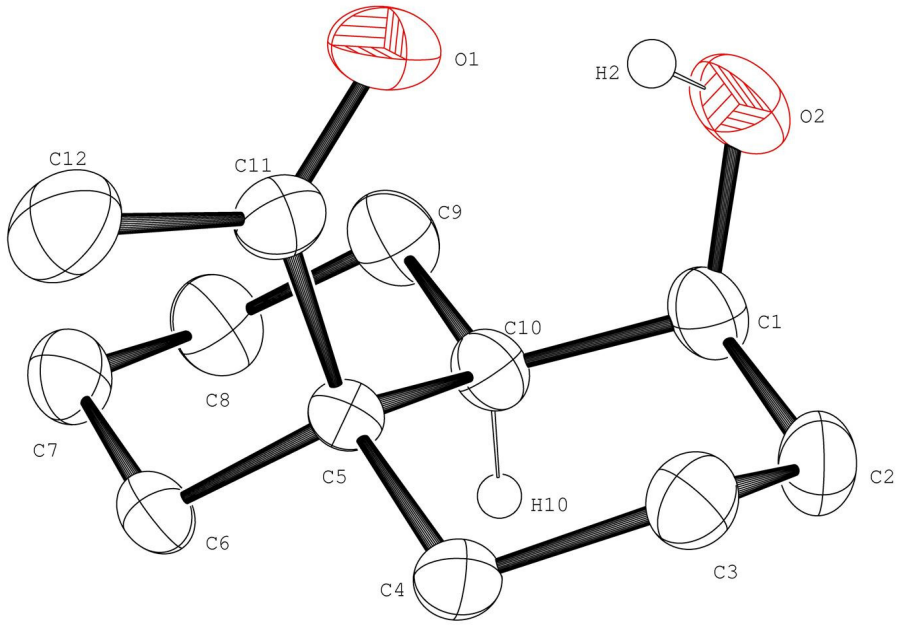
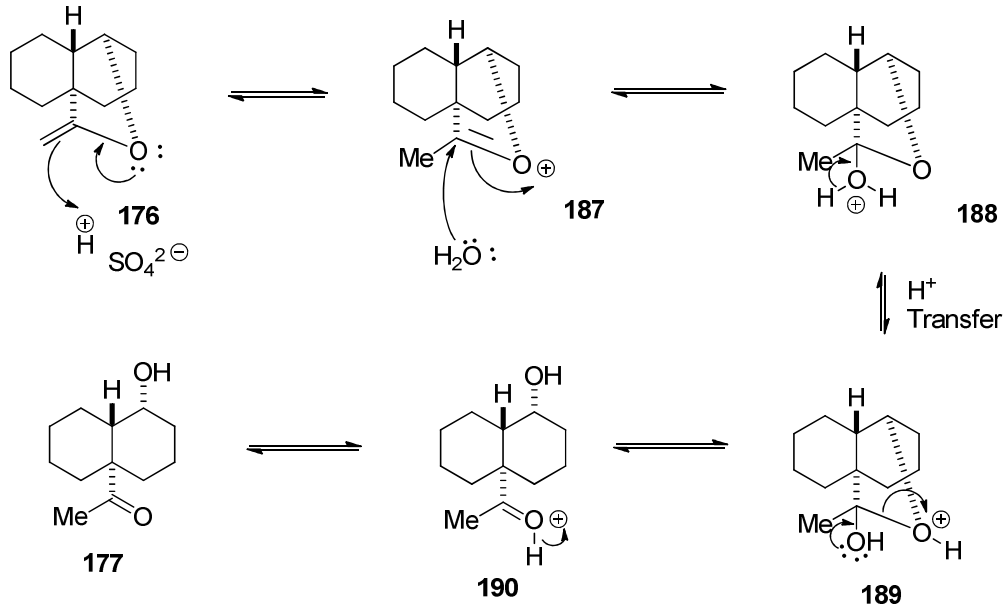


Figure 2.2 ORTEP diagram of 177, ellipsoids at 50% probability. Selected H atoms are shown as spheres of arbitrary radius.

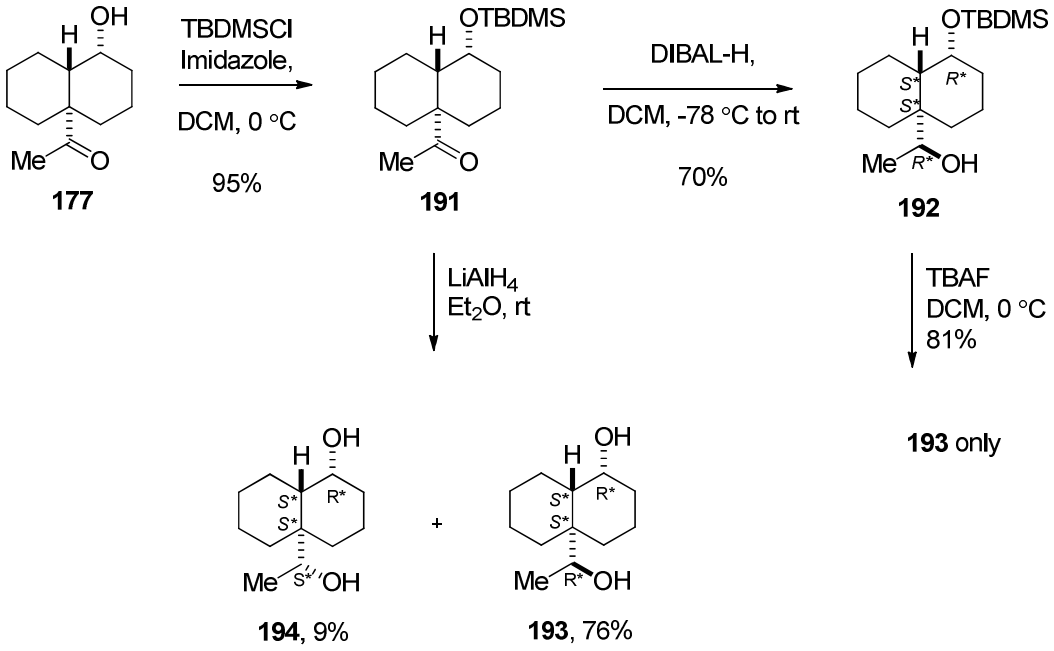
Gentle reflux of the vinyl ether in dilute sulfuric acid, in presence of diethyl ether, undergoes ring opening reaction *via* a typical enol ether hydrolysis mechanism (Scheme 2.21). However ring opening by refluxing in a dilute aqueous acid in absence of organic solvent (and hence at a higher temperature) goes *via* an S_N2 mechanism giving the *trans*- product.



Scheme 2.21 Ring opening mechanism of the vinyl ether 176 under mild conditions.

Interestingly, the ring opening reaction could never be induced to go to completion and yields were never higher than 51%. The idea of a reversible process was then considered. Pure hydroxyl ketone **177** was resubjected to the same reaction conditions as for the enol ether hydrolysis. After refluxing it for several hours, characteristic peaks of vinyl ether **176** were detected by proton NMR. This confirmed the ring opening reaction of the **176** is reversible.

In order to effect conversion of the functionality in **177** to the desired vinyl ketone **135,** alcohol protection as a silyl ether was required. The desired OTBDMS product (**191**) was formed in excellent yield (Scheme 2.22). Further reduction with DIBAL-H furnished (**192**) as a single diastereomer in 70% yield. In order to assign the relative configuration of newly formed stereocentre, silyl ether **191** was reduced with $LiAlH_4$ followed by an acidic workup, resulting a mixture of two diastereoisomeric diols (**193**) and (**194**). The major diol **193** was formed in a ratio of 12.6:1 to the **194** and was identical to the material produced by deprotecting silyl ether **192** with TBAF in 81% yield.



Scheme 2.22 Synthesis of the diols 193 and 194.

The relative stereochemistry of **193** was established by X-ray crystallography (Figure 2.3).

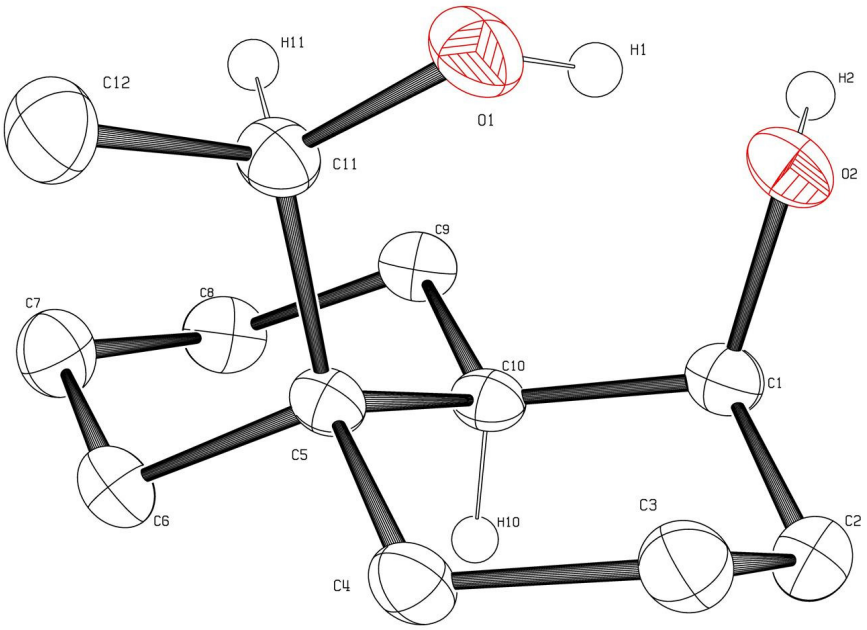
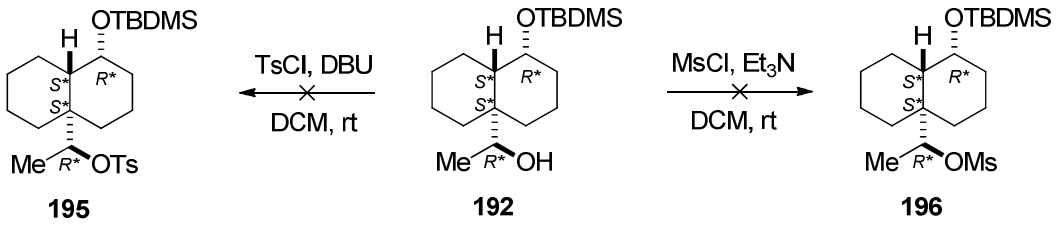


Figure 2.3 ORTEP diagram of 193, ellipsoids at 50% probability. Selected H atoms are shown as spheres of arbitrary radius.

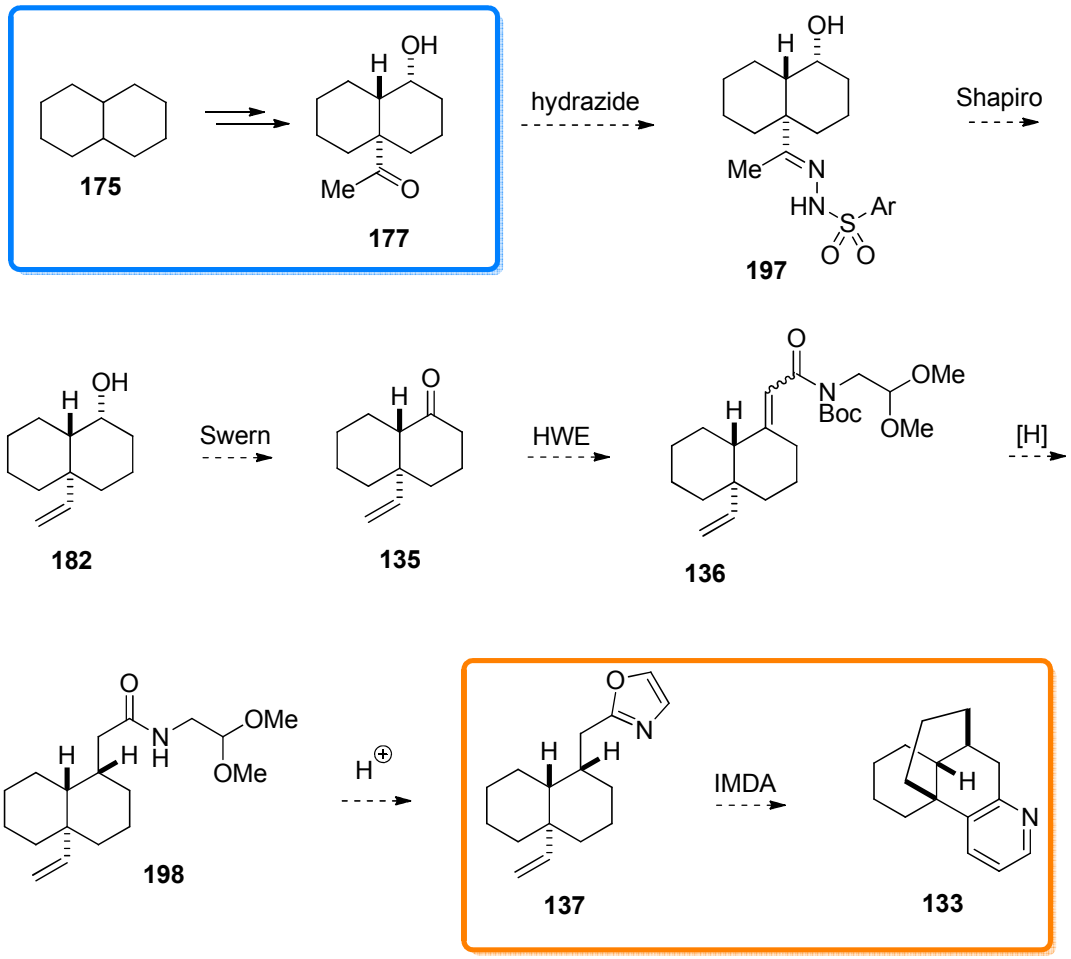
Attempts to sulfonylate the alcohol **192** in order to effect elimination to the desired vinyl derivative were not successful (Scheme 2.23), most likely due to the poor accessibility of the neopentylic hydroxy group.



Scheme 2.23 Attempts to sulfonylate the alcohol 192.

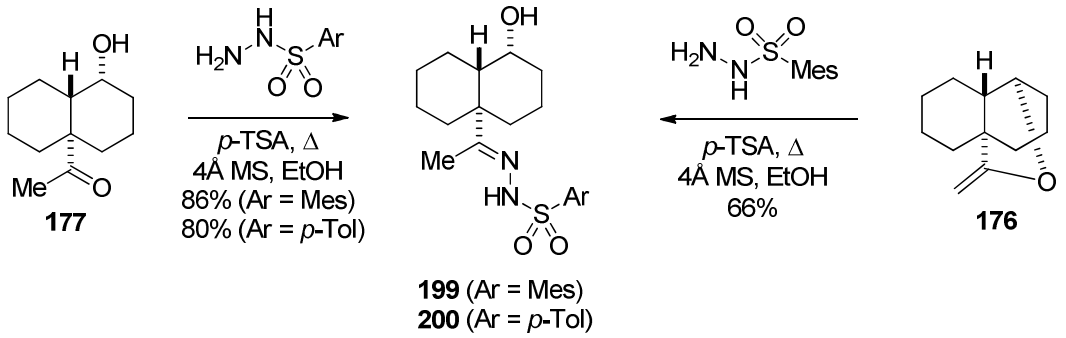
2.2.3 Shapiro reaction

An alternative approach to access the vinyl moiety in the target system was required, which led us to modify the 2nd generation approach. The 3rd generation approach (Scheme 2.24) uses the same hydroxy ketone **177** to access a sulfonylhydrazone (**197**), which could be transformed to the target vinyl alcohol **182** by means of a Shapiro reaction.[71] The alcohol **182** could then be oxidised to the corresponding ketone **135** and be used in further steps as envisaged for the 1st and 2nd generation approaches. Steps highlighted in blue indicate reactions previously accomplished.



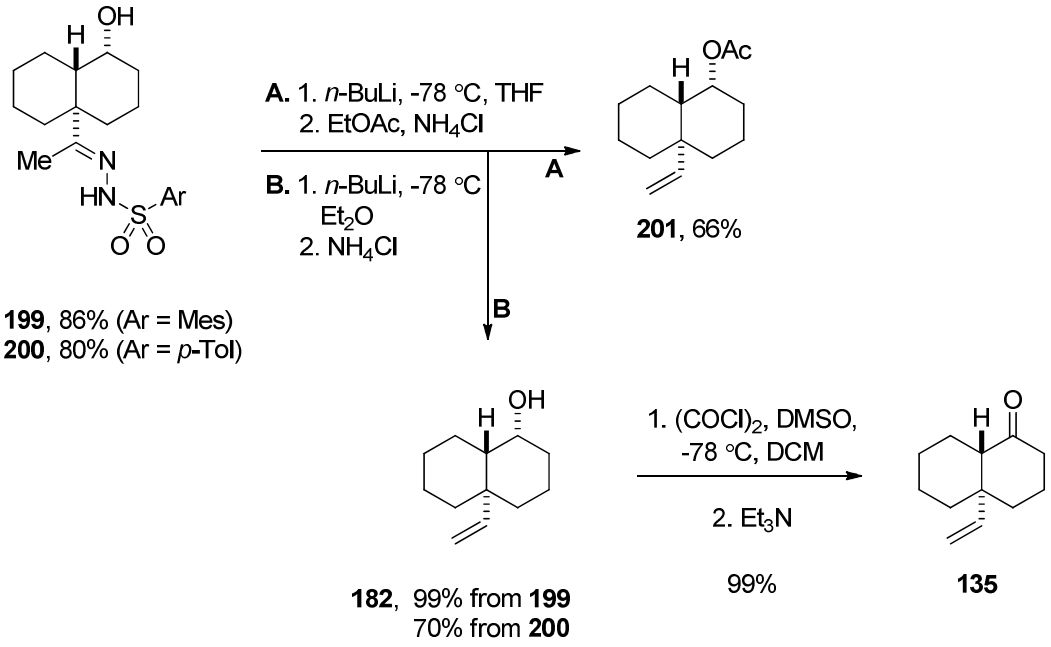
Scheme 2.24 3rd generation approach *via* Shapiro reaction.

Treatment of hydroxy ketone **177** with mesitylenesulfonylhydrazide in the presence of a catalytic amount of *p*-TSA afforded hydrazone (**199**) in 86% yield (Scheme 2.25). Reaction of **177** with *p*-toluenesulfonylhydrazide under the same conditions yielded the corresponding hydrazone (**200**) in good yield, however separation of this product from the reaction mixture proved to be more challenging due to the solubility of the product.



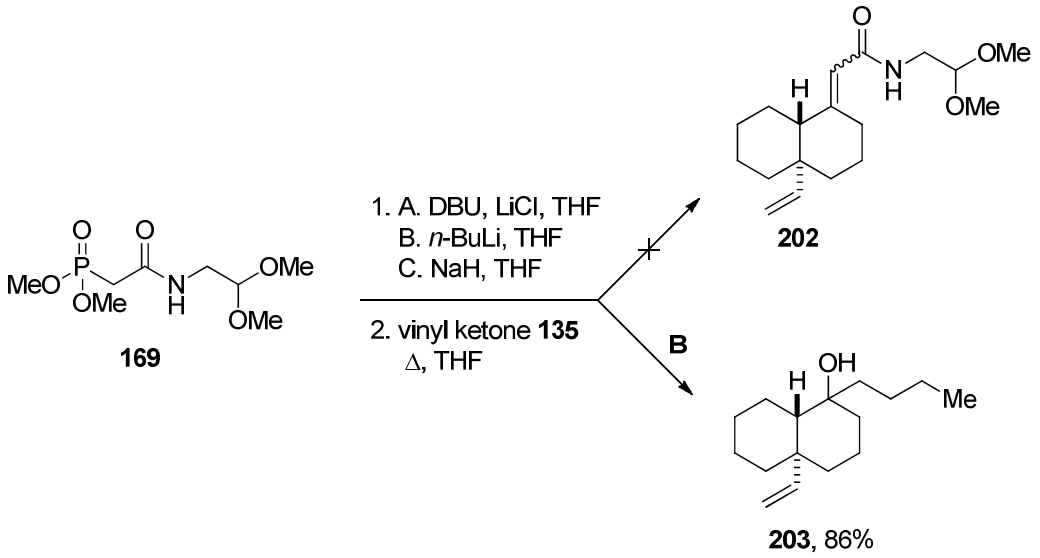
Scheme 2.25 Formation of hydrazones 189 and 190.

As vinyl ether **176** undergoes a ring opening reaction under acidic conditions producing hydroxy ketone **177**, and hydrazone formation also involves acidic catalysis, the idea of a one pot synthesis of **199** from **176** occurred. It was found that the reaction indeed proceeded smoothly, using 10 mol% of *p*-TSA, giving hydrazone **199** in 66% yield (Scheme 2.26). Successful formation of hydrazones provided substrates for the Shapiro reactions. The first attempt at the reaction of **199** in THF involved exposing it to three equiv. of *n*-butyllithium, followed by protic quench and dilution of the reaction mixture with EtOAc, which led to inadvertent acetylation of the formed vinyl alcohol to give (**201**) in 66% yield as the sole product (Scheme 2.26). Repeating the reaction using water-immiscible diethyl ether as reaction solvent in place of THF, followed by protic workup, produced vinyl alcohol **182** in excellent 99% yield. Three equivalents of base were needed due to the presence of a free hydroxy group. Hydrazone **200** yielded the alcohol **182** in lower yield due to the presence of impurities (unreacted tosylsulfonylhydrazide) in the substrate. From vinyl alcohol **182**, vinyl ketone **135** was accessed by Swern oxidation, delivering the product in 99% yield.



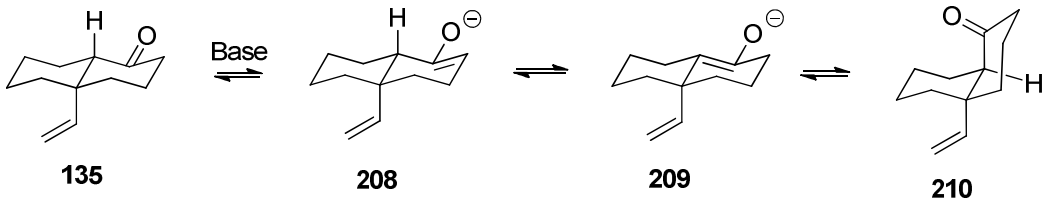
Scheme 2.26 Synthesis of vinyl ketone 135 *via* Shapiro reaction.

Access to the vinyl ketone **135** provided the opportunity to realize the olefination step envisaged in the 1st and 2nd generation approaches. To access olefin (**202**), ketone **135** was employed in HWE conditions with phosphonoacetamide **169**. None of the attempted conditions gave the desired α,β-unsaturated amide **202**. Changing the temperature, reaction time, or base, or use of DBU and LiCl as per the Masamune–Roush modification[63] did not produce the olefination product. When butyllithium was used, an undesired 1,2 addition of the butyl fragment occurred, generating (**203**) (Scheme 2.27). Use of non-nucleophilic NaH did not afford any product.



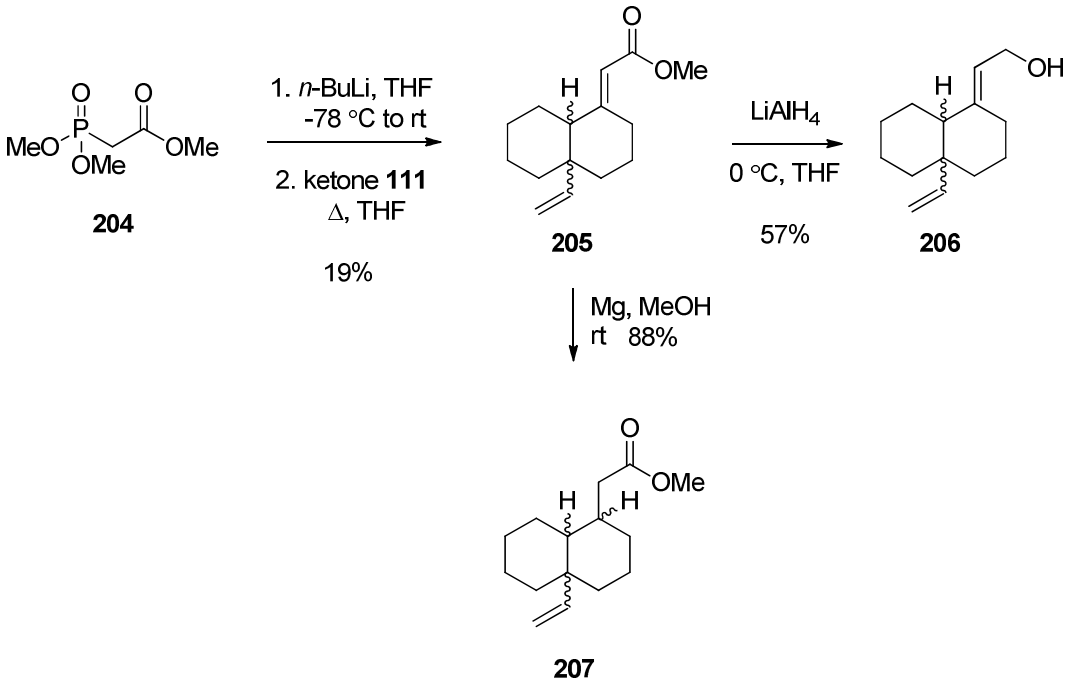
Scheme 2.27 HWE reaction of the phosphonoacetamide 169.

It was decided to employ a less functionalised phosphonate in the Horner–Wadsworth–Emmons reaction, with the intention of introducing an oxazole precursor in additional, subsequent steps. Thus, the phosphonoacetamide **169** was changed to methyl 2-(dimethoxyphosphoryl)acetate (**204**). After deprotonation with *n*-BuLi and reflux for 64 h, the reaction afforded the desired product, alongside formation of the epimerised material (**205**). During the reflux under basic conditions, decalinone ring isomerisation occurred whereby the *trans*-decalin ring epimerised to *cis*-decalin (**210**) (Scheme 2.28) which then underwent reaction with the phosphonate nucleophile to form the epimerised product.



Scheme 2.28 *Trans*- to *cis*- epimerisation of vinyl ketone 135.

As the separation of α,β-unsaturated esters was not possible by means of chromatography, it was decided to carry the mixture forward to the reduction step and separate the products later in the synthesis. Common reducing agents such as $NaBH_4$ and *L*-selectride did not effect conjugate reduction of the unsaturated ester **205** (Scheme 2.29). $LiAlH_4$ reduction did not favour 1,4 addition of the hydride and instead derived the alcohols **206** as anticipated.



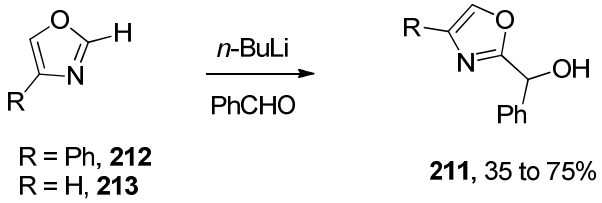
Scheme 2.29 HWE reaction of methyl 2-(dimethoxyphosphoryl)acetate 204.

Hudlicky *et al.*[72] published the successful reduction of α,β-unsaturated esters using single electron transfer (SET) employing Mg in MeOH. The reaction with unsaturated ketone **205** was successful. However, using starting material as a mixture of 2 epimers, the reaction produces all four possible diastereoisomeric products (**207**) (Scheme 2.29). The separation of these proved to be impossible. NMR data of the mixture were very complex; we could not unambiguously assign each of the products and the ratios between each diastereomer.

2.2.4 Attempts at oxazole introduction not employing an aldehyde

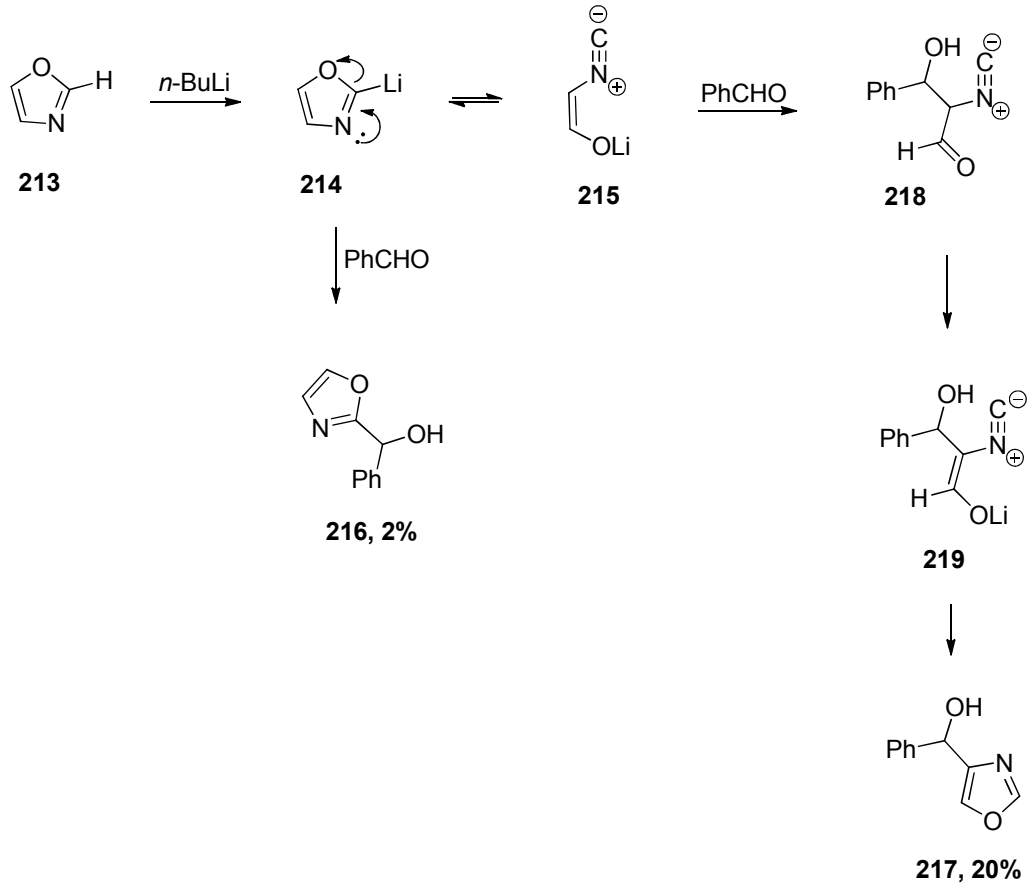
There is not much literature precedent for the synthesis of 2-substituted 4,5-unsubstituted oxazoles, as mentioned above. Therefore, we gave consideration to an alternative approach, namely that of introducing an intact oxazole to the decalin skeleton

Rickborn *et al.* reported formation of (**211**), with yields increasing from 35% to 75% upon the reaction time of oxazoles (**212**) with benzaldehyde being increased from 0.25 h to 24 h (Scheme 2.30).[73]



Scheme 2.30 Reaction of oxazoles 212 with benzaldehyde.

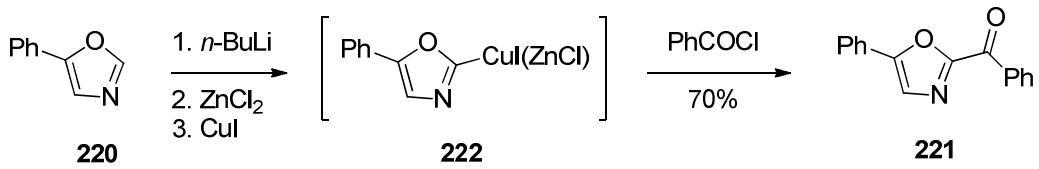
On attempts to trap 2-lithiooxazoles with electrophiles, a complication arises due to an equilibrium between the lithiated oxazole product (**214**) and the ring-opened isocyanide (**215**) (Scheme 2.31).[73-76] Prolonged reaction time allows adducts derived from the acyclic tautomer **215** to form, as this is in equilibrium with the precursor of cyclic C-2 product (**216**). In a similar manner, Hodges *et al*. found that after 24 h, reaction of lithiated oxazole with benzaldehyde gave only 2% of **216**, alongside 20% of the 4-substituted oxazole (**217**) which arises from transformation of (**218**) to (**219**) followed by cyclisation.[74]



Scheme 2.31 Metalation at C-2 of oxazole and reactivity with benzaldehide.

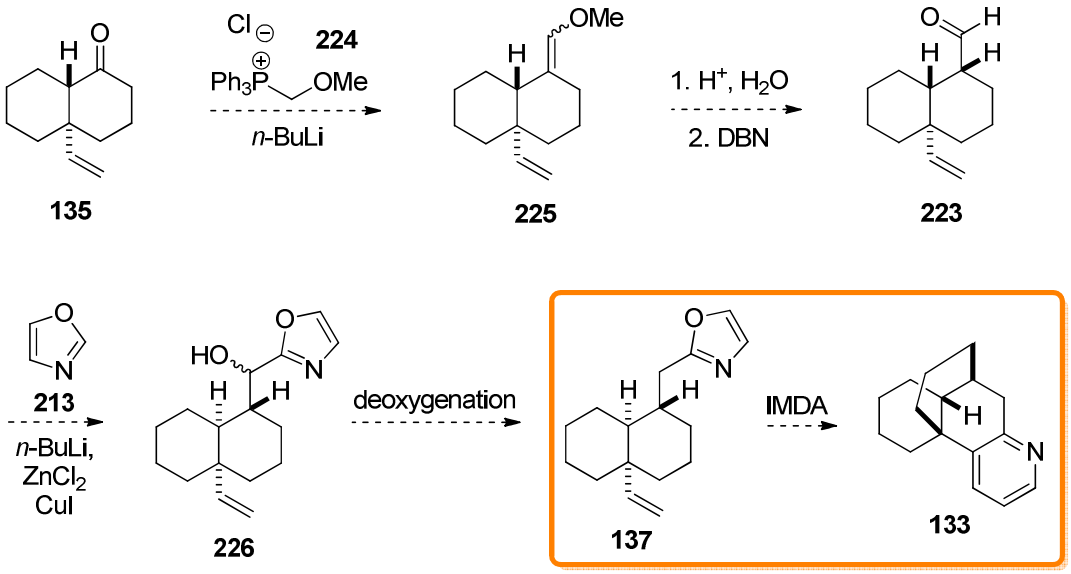
Anderson *et al.* further investigated acylation of 5-phenyloxazole (**220**) at the C-2 position in reactions with acid chlorides.[77] Deprotonation of 5-phenyloxazole **220** and reaction with benzoyl chloride gave a sole reaction product (**221**) (Scheme 2.32).[73] According to the authors, addition of zinc (II) chloride solution to the resulting lithiated oxazole yields the corresponding zinc species, which are unreactive towards benzoyl chloride even at elevated temperatures. Addition of 1 equiv. of copper (I) iodide to the organozinc derivative leads to the generation of bimetallic species (**222**), which reacts rapidly at room temperature to furnish the ketone **221** in 70% yield. The authors also state that careful monitoring of the reaction mixture provided no evidence of formation of products arising from the ring-opened tautomer. Direct transmetallation of lithiooxazole with copper (I) iodide only, led to the generation of species which failed to

deliver either the ketone **221** or the opened ring product when reacted with benzoyl chloride.[77]



Scheme 2.32 Improved synthesis of 221 using bimetallic oxazole intermediate.

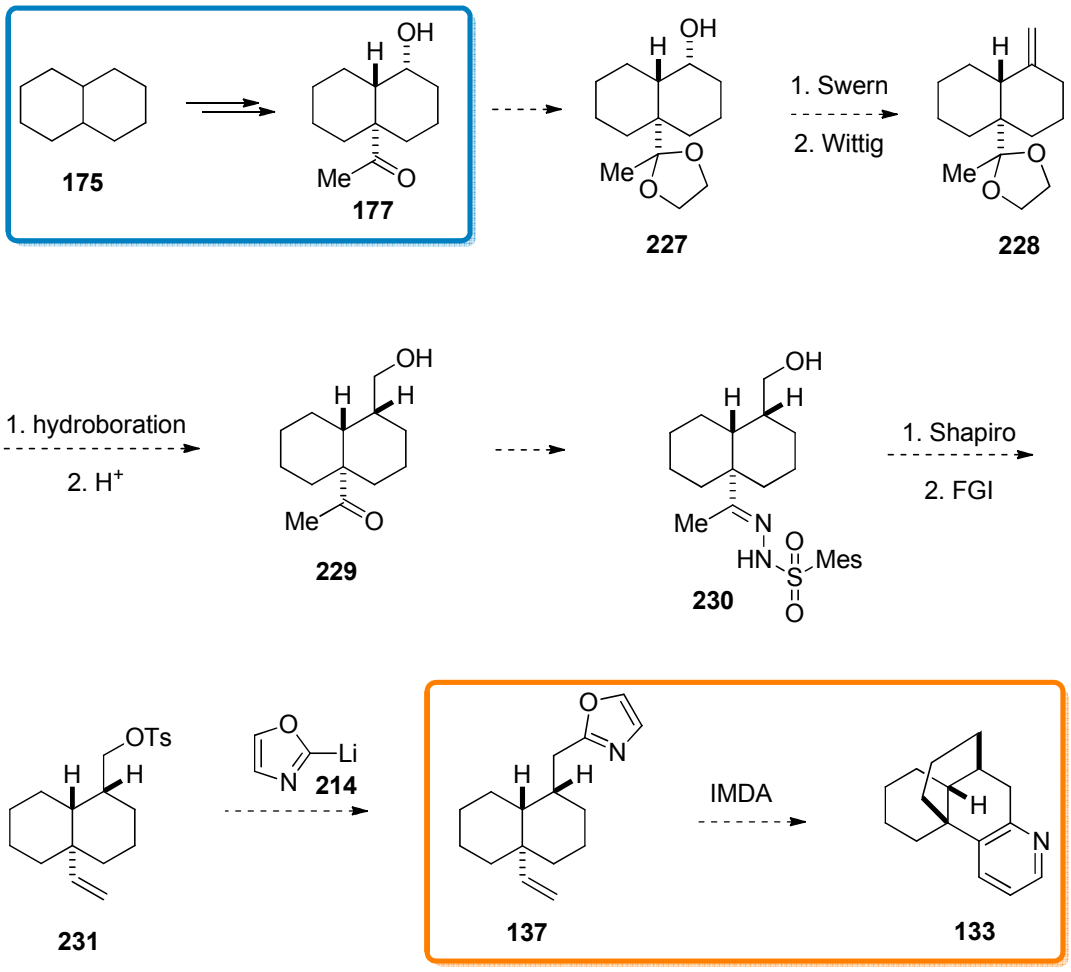
These findings were considered to be useful in the context of a reaction of aldehyde (**223**) with metallated oxazole **214** as planned in our 4th generation approach (Scheme 2.33). To access aldehyde **223**, use of a Wittig reaction with (methoxymethyl)triphenylphosphonium chloride (**224**) was considered. Subsequent hydrolysis of the resultant olefination product (**225**) would give a mixture of aldehydes from which the desired epimer **223** should be isolable; epimerisation with 1,5-diazabicyclo[4.3.0]none-5-ene would allow recycling of the undesired epimer.



Scheme 2.33 4th Generation approach *via* coupling of aldehyde 223 with 2-oxazolyl cuprate.

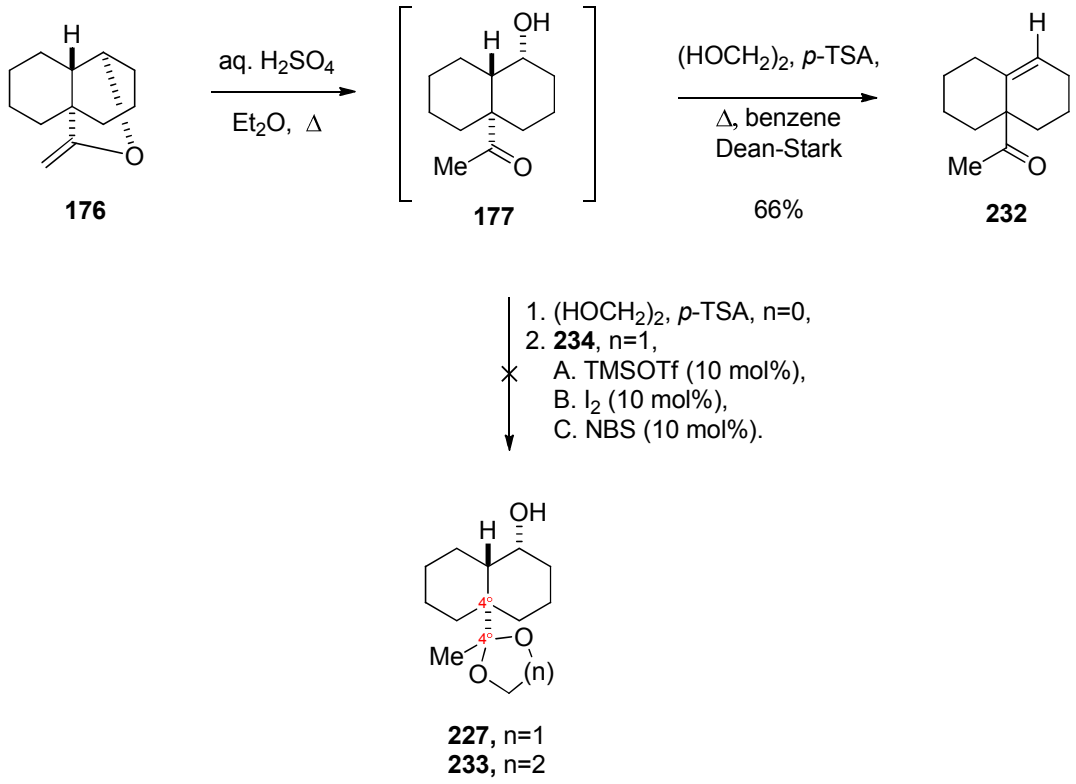
Attempts at one-carbon homologation *via* Wittig reaction were fruitless. After stirring a reaction mixture of ketone **135** and *in situ* generated ylide overnight, the reaction failed to occur. Most of the unreacted starting material was recovered.

In order to effect the one-carbon homologation, a new approach was envisaged. This 5th generation approach would involve protection of the hydroxy ketone **175** to give ketal (**227**) (Scheme 2.34). Subsequent oxidation of **227** to the corresponding ketone would provide a substrate for an olefination reaction to access alkene (**228**). Then hydroboration of **228**, furnishing alcohol, followed by ketal deprotection, would furnish homologated hydroxy ketone (**229**). Next we proposed formation of a hydrazone (**230**) followed by a Shapiro reaction, which was successful in previous reactions to introduce the vinyl moiety. Introduction of oxazole would occur *via* displacement of tosylate (**231**). Successful formation of **137** would provide the substrate for IMDA as anticipated in previous approaches to access compound **133**.



Scheme 2.34 5th Generation approach *via* hydroboration of 228 and coupling of tosylate 231 with lithiated oxazole.

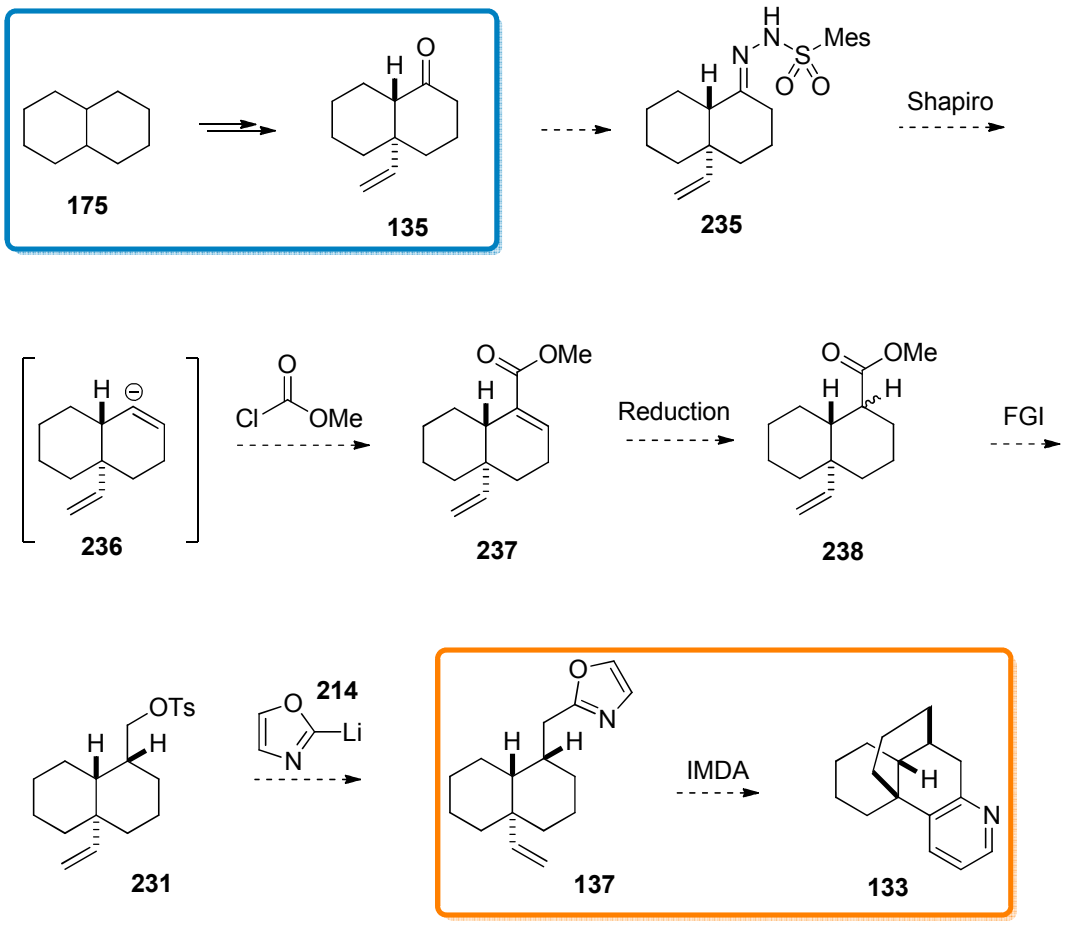
On the basis of the approach outlined, to avoid double olefination, the ketone must be protected. A direct approach to ketal formation from vinyl ether **176** was attempted. As the enolate undergoes the ring opening step forming hydroxy ketone **177**[78,79] catalysed by acid, subsequent further ketal synthesis was performed using standard procedure[80] (Scheme 2.35). Reaction mixture was vigorously stirred at rt for 2 days in DCM. A partial reaction was observed; formation of product was detected by mass spectrometry and characteristic proton peaks were observed by NMR. However the amount of ketal formed was small.



Scheme 2.35 Attempted formation of the acetal 227.

The reaction mixture was then refluxed for an additional 15 h, but the increase in temperature had no effect. When the reaction mixture was refluxed in benzene using a Dean–Stark apparatus[81], only elimination product (**232**) was formed, in good yield (Scheme 2.35). Various modifications of classical ketal formation were attemped. Addition of 5 mol% of molecular iodine[82] had no effect on synthesising (**233**). Use of 1,3-bis(trimethylsiloxy)propane (**234**) and TMSOTf[83], iodine[84], or NBS[85] were equally unsuccessful. Examining the structure of the targeted ketals **227** and **233**, it can be seen that there are two adjacent quaternary carbons. The resultant steric hindrance likely explains such poor reactivity.

In light of the failure of the ketalisation, a modified 6th generation approach was conceived (Scheme 2.36).

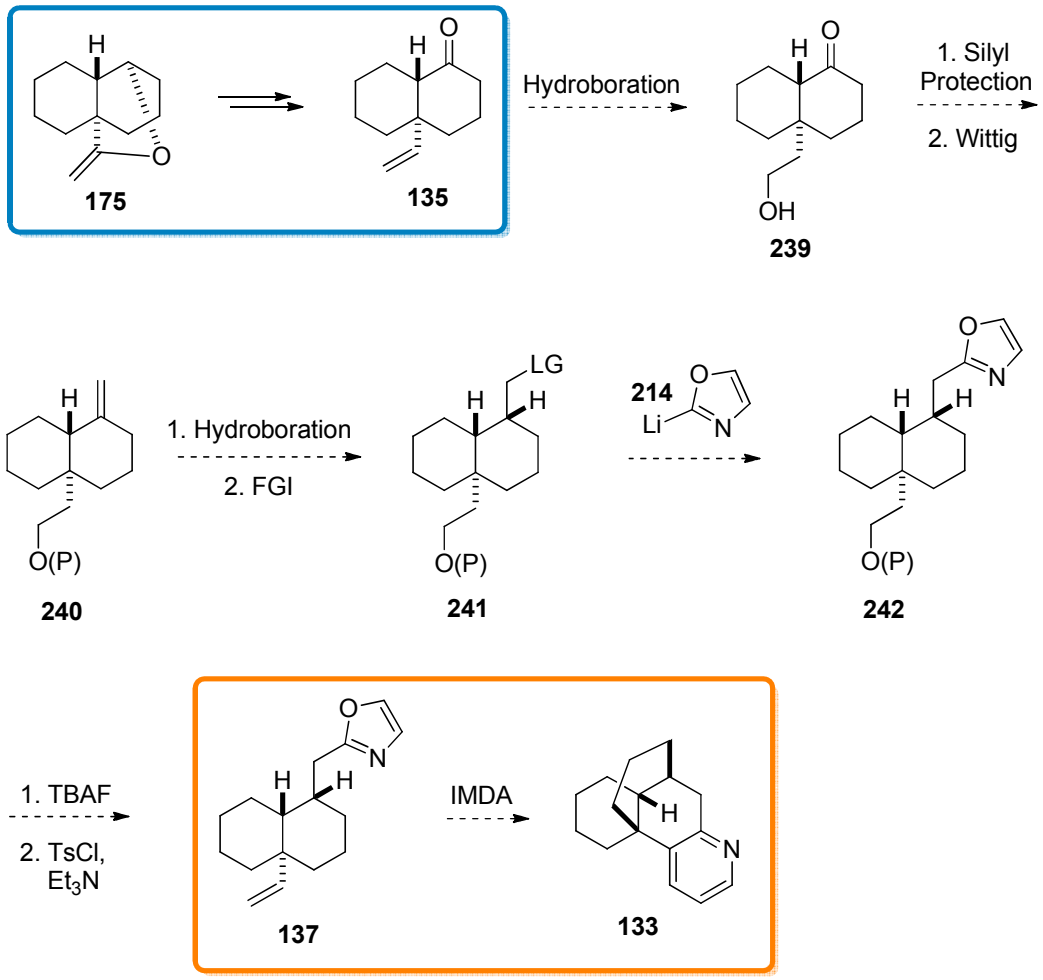


Scheme 2.36 6th Generation approach *via* second Shapiro reaction.

The Shapiro reaction had proven useful in previous approaches and the idea of forming the tosylate (**231**) *via* second Shapiro reaction arose. Formation of hydrazone (**235**) from vinyl ketone **135** would provide the precursor for a second Shapiro reaction. The carbanionic intermediate (**236**) of this reaction would then be trapped with methyl chloroformate to furnish an α,β-usaturated system (**237**). Further reduction would give (**238**), which could be converted to vinyl tosylate **231**. Introduction of the oxazole moiety to compound **231** would afford the desired IMDA precursor **137** which would be employed in further steps as per the previous plans. However, attempts to react vinyl ketone **135** with 2,4,6-trimethylbenzenesulfonohydrazide were unsuccessful, plausibly due to steric hindrance of the ketone.

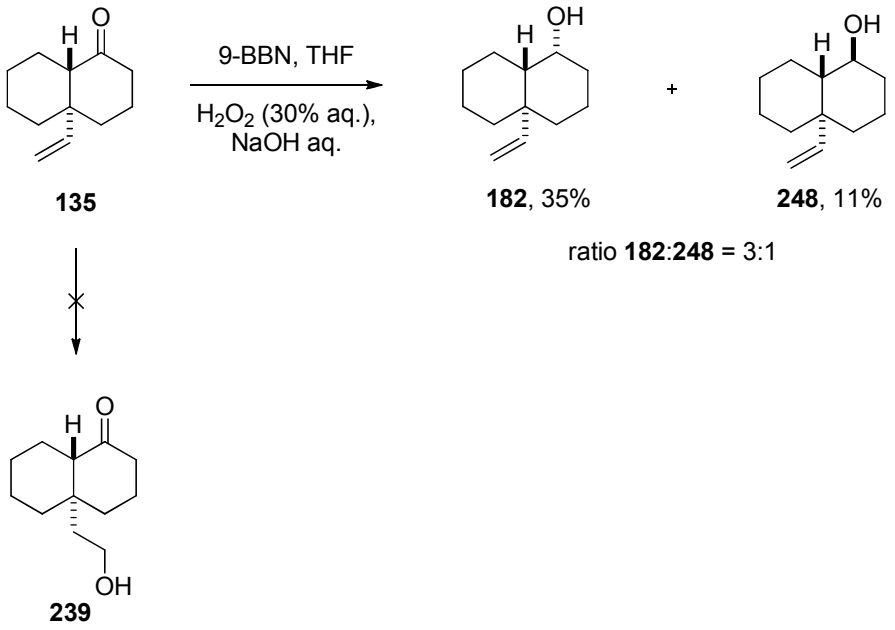
2.2.5 Regioselective hydroboration

A new strategy was designed in order to access IMDA precursor **137** (Scheme 2.37). The new 7th generation approach involved hydroboration of vinyl ketone **135** with 9-BBN to access alcohol (**239**), which would be protected with a silicon-based protecting group providing the ketone. Olefination to the corresponding alkene (**240**) followed by a second hydroboration would afford the 1-carbon homologated alcohol. Subsequent derivatisation of (**241**) and displacement with metallated oxazole would introduce the desired oxazole moiety, giving (**242**). Then deprotection of **242** followed by transformation of the alcohol to the corresponding tosylate followed by treatment with base would give elimination product **137**. Successful formation of substrate for IMDA will provide access to precursor for the key reaction of our approach as anticipated to access compound **133**.



Scheme 2.37 7th Generation approach *via* double hydroboration.

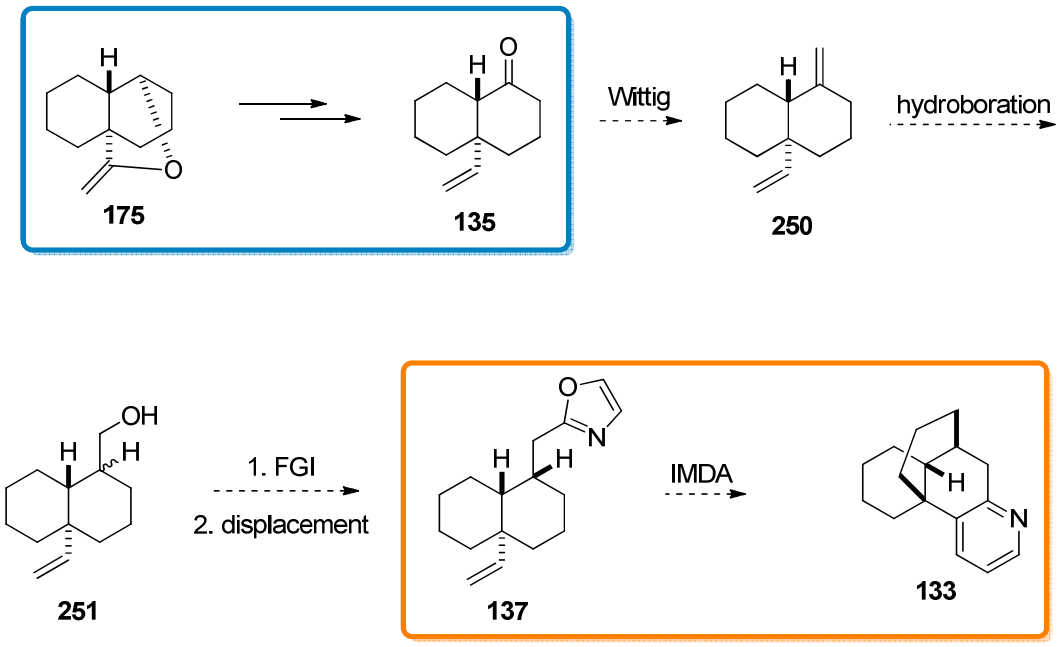
A previously prepared vinyl ketone **135** was introduced to the hydroboration reaction using 9-BBN. After the reaction was completed (as indicated by the absence of starting material on TLC) and product purified by chromatography, we observed characteristic vinylic proton peaks in the ^{1}H-NMR spectrum. To our surprise, the vinyl group is inert to hydroboration with 9-BBN. In fact this reagent acted as a reducing agent yielding a mixture of two alcohols **182** and its epimer (**248**) in a total of 46% yield (Scheme 2.38). The ratio of the two products was 3:1.



Scheme 2.38 Hydroboration of vinyl ketone 135.

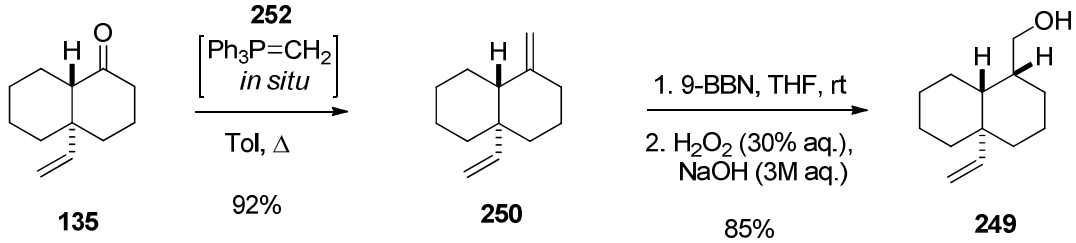
The serendipitous discovery of the inertness of the vinyl group with respect to hydroboration permitted us to modify the 7th generation approach and propose accessing the homologated vinyl alcohol (**249**) *via* a simple two-step sequence as envisaged in the 8th generation approach (Scheme 2.39).

This approach employs hydroboration of a bis(alkene) (**250**), which can be accessed from vinyl ketone **135** by means of olefination. Subsequent hydroboration of **250** would yield the mixture of diastereomeric alcohols (**251**). Finally isolation of the desired diastereomer, followed by tosylation would form the precursor for two further steps exactly as envisaged in the 6th and 7th generation model systems.



Scheme 2.39 8th Generation approach *via* hydroboration of the bis(alkene) 250.

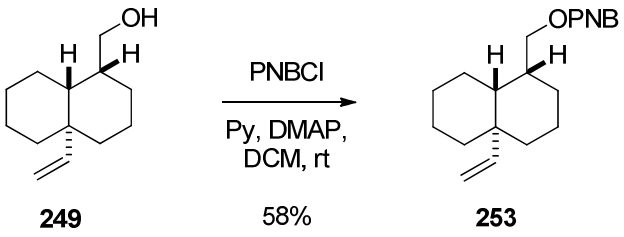
The Wittig methylenation of ketone **135** to synthesize bis(alkene) **250** was tested. Reaction with ylide (**252**), generated *in situ* from methyltriphenylphosphonium bromide, yielded the desired product in good yield (Scheme 2.40).



Scheme 2.40 Synthesis of homologated vinyl alcohol 249.

The best results for this olefination reaction were achieved when using potassium *tert*-butoxide as a base. Reactions using *n*-BuLi gave lower yields of the alkene **250** alongside formation of the product derived from epimerisation at the ring junction.

Hydroboration of the olefin **250** with 9-BBN proceeded smoothly giving a *single* product of the reaction in 85% yield. This remarkable transformation proved to be totally regio- and diastereoselective, providing us with the desired diastereomer **249** (Scheme 2.40). To confirm the relative stereochemistry of the hydroboration product, the esterification of the vinyl alcohol **249** was undertaken to obtain the *p*-nitrobenzoate ester (**253**) in 58%, with the intention of obtaining crystals of suitable quality for x-ray diffraction.

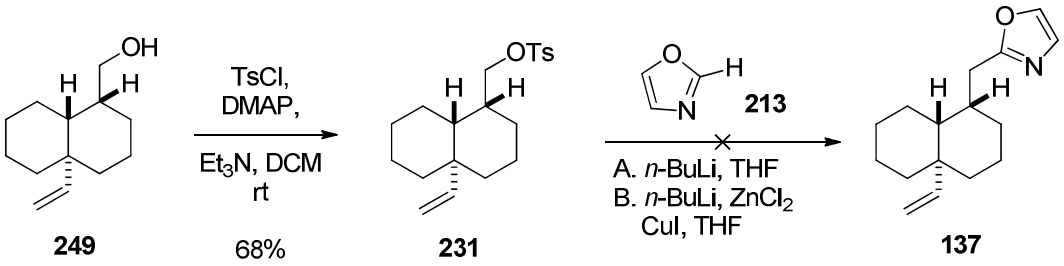


249 58% **253**

Scheme 2.41 Formation of PNB ester 253.

Unfortunately, no such crystals were obtained; the relative configuration was subsequently supported by the basis of NOESY NMR data of an aldehyde derivative (*vide infra*).

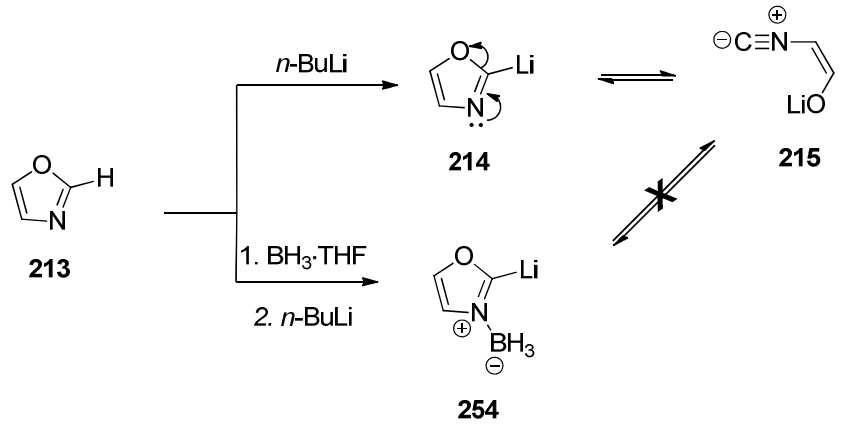
Vinyl alcohol **249** was submitted to tosylation to give derivative **231** in 68% yield (Scheme 2.42). To test the oxazole displacement reaction, tosylate **231** was introduced to the lithiated oxazole **214**. Unfortunately only starting material was recovered. Attempted oxazole alkylation at C-2 position using a copper-mediated reaction, applying methodology developed by Anderson,[77] did not work either.



249 231 137

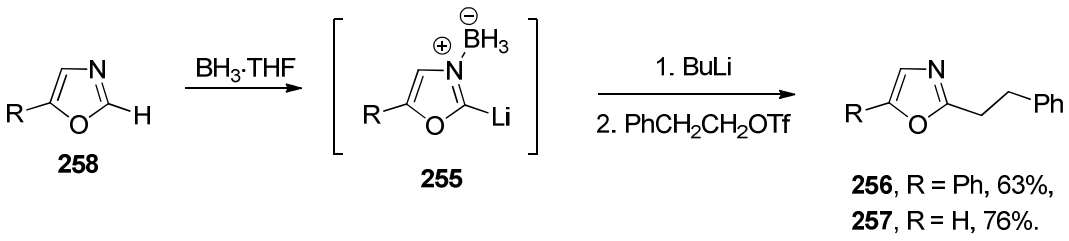
Scheme 2.42 Attempted synthesis of the vinyl oxazole 137 by displacement of tosylate 231.

In the literature, Vedejs and Monahan[86] and Boger *et al.*[87] report accessing 2-alkylated oxazoles using lithiated oxazole complexed to borane (**254**), by displacement of triflates. Vedejs described metallation of oxazole-borane complexes as a practical solution to the problem of ring opening of 2-lithiooxazoles (Scheme 2.43).[88]



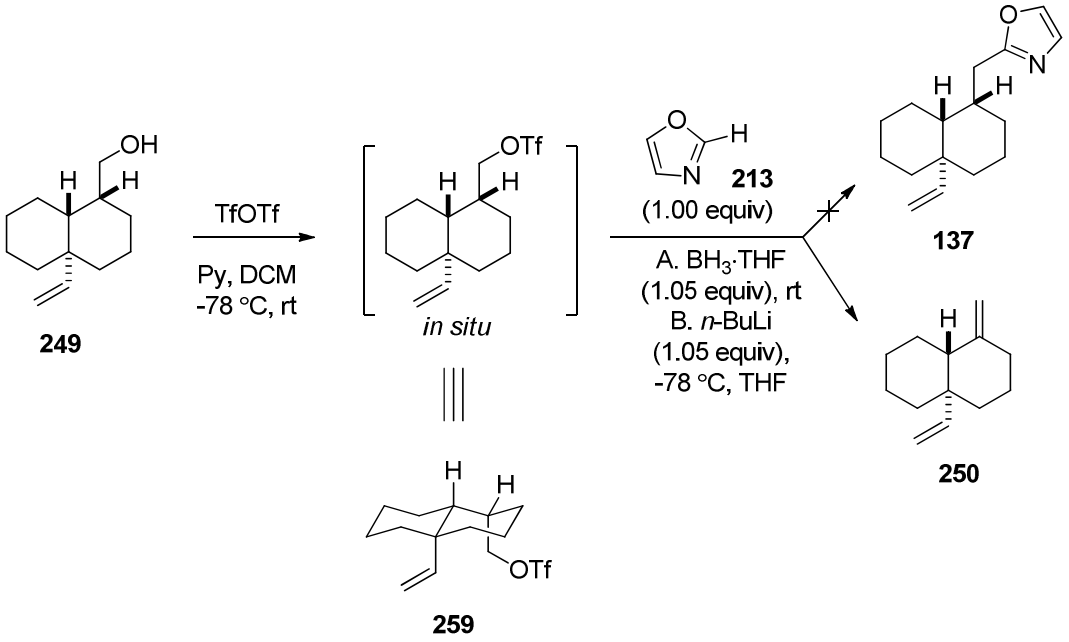
Scheme 2.43 Use of borane complexation to prevent oxazole ring opening, as reported by Vedejs.

Treatment of lithiated oxazole-borane complexes (**255**) with alkyl triflates reportedly affords alkylated products (**256**) and (**257**) in good yields after purification (Scheme 2.44).



Scheme 2.44 Metallation of oxazole-borane complexes and their alkylation, as reported by Vedejs.

Attempts at the reactions of our corresponding tosylate **231** and triflate (**259**) under the same displacement conditions were unsuccessful, resulting only in elimination to the bis(alkene) **250** in both cases (Scheme 2.45).

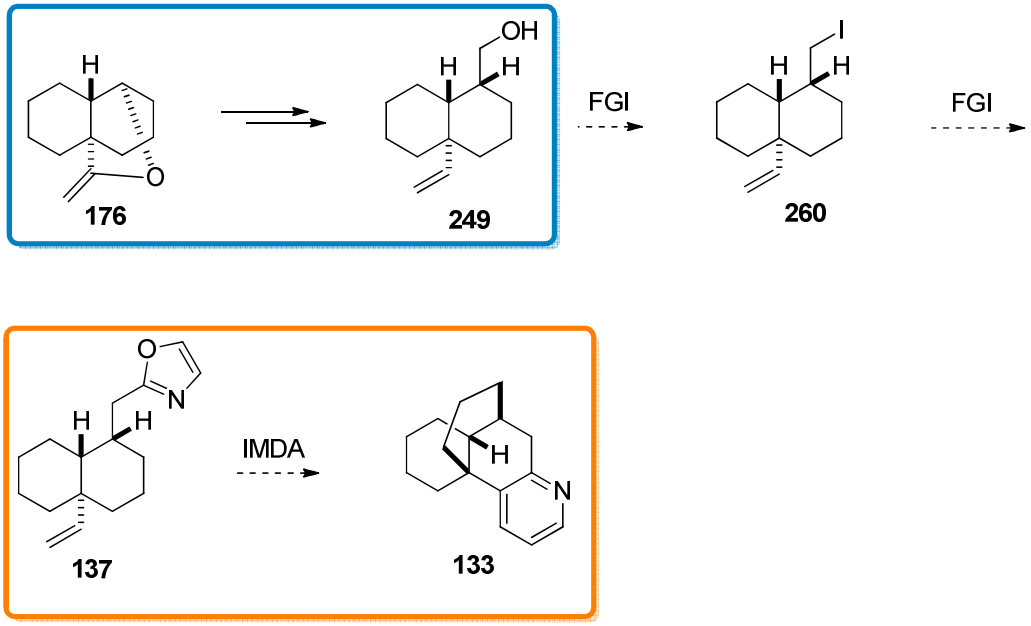


Scheme 2.45 Synthesis of triflate 259 and attempted displacement with lithiated oxazole-borane complex.

Despite the leaving group being on a primary carbon, steric hindrance of the molecule will most likely explain these results. S_N2 displacement requires

approach of the nucleophile at 180º angle; there is a high probability this requirement cannot be fulfilled in the case at hand.

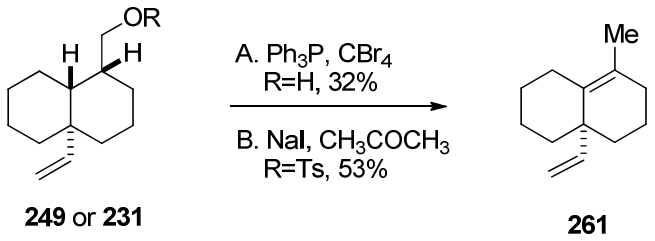
Negative results for the displacement of tosylate **231** and triflate **259** left us with a last option envisaged in this series of reactions. A slight modification of the previous approach would allow formation of the iodide (**260**), which should be easily accessible from alcohol **249**. A successful reaction of this iodide with metallated oxazole would provide the desired substrate for IMDA as envisaged in previous approaches (Scheme 2.46).



Scheme 2.46 9th Generation approach *via* displacement of iodide 260.

The initial attempt to access iodide from alcohol **249** commenced with the use of a classical Appel reaction[89] to access corresponding bromide which would undergo a Finkelstein reaction[90] to give the corresponding iodide (Scheme 2.47). In the event, the substrate undergoes elimination, providing elimination product (**261**) alongside recovery of unreacted starting material. This may have arisen *via* formation of the bis(alkene) **250** which then rearranged to the tetra-substituted alkene **261**. The same results were observed when tosylate **231** was treated with NaI in acetone in order to perform functional group

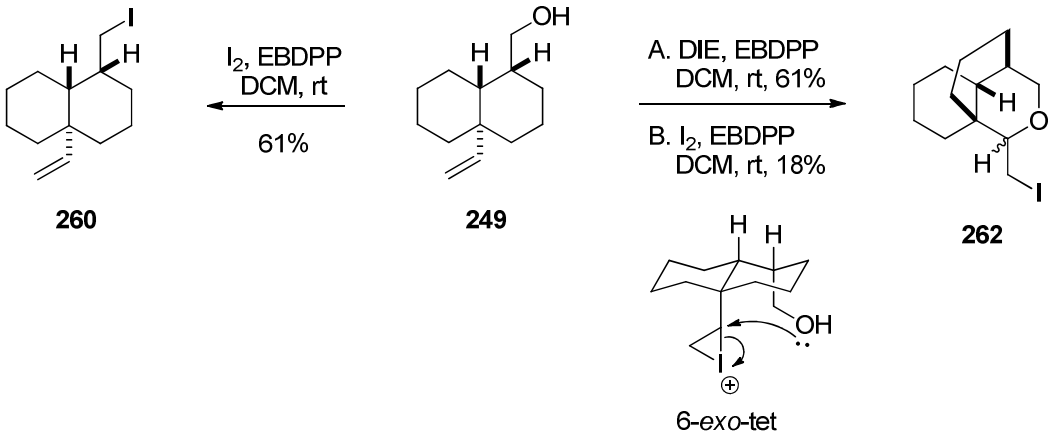
displacement to access iodide **260**. This isomerisation was not observed in other cases of elimination.



249 or **231** **261**

Scheme 2.47 Formation of tetrasubstituted alkene elimination product 261.

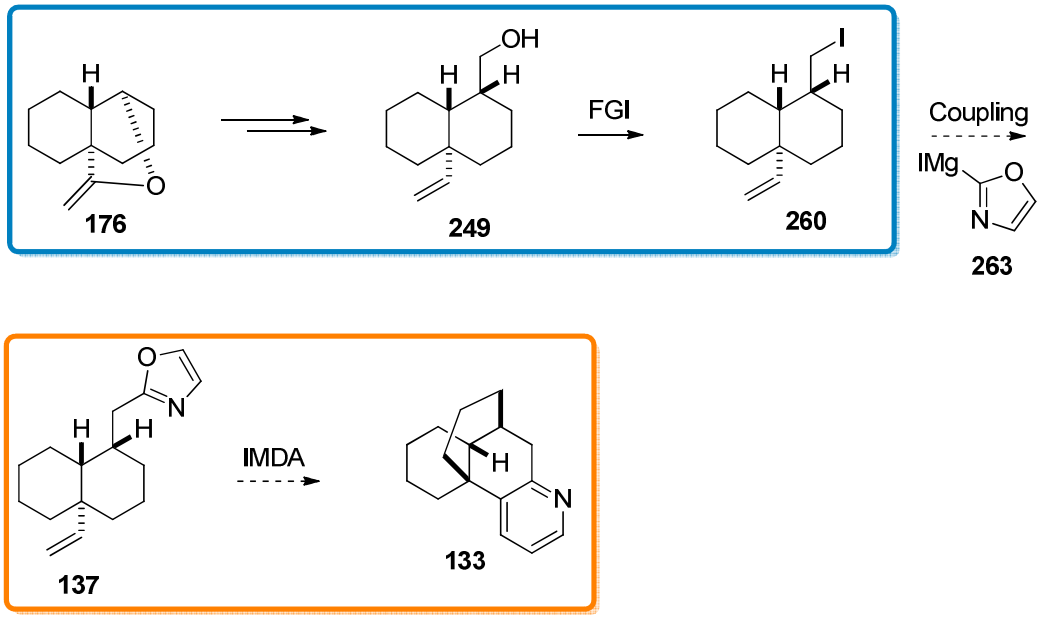
Functional group interconversion by displacement of hydroxy group with iodide eventually proved to be possible. However, the synthesis of the required iodide did not prove to be easy due to poor stability of the product and difficulty in separating it from triphenylphosphine and its oxide. Column chromatography cannot be used as immediate elimination occurrs to the bis(alkene) **250**. Use of ethylenebis(diphenylphosphine) instead of triphenylphospine was found to be advantageous due to easier separation of the product from the phosphorus-containing byproducts.[91,92] Reaction of reactive iodide species with the alcohol provided desired iodo derivative **260** in 61% yield (Scheme 2.48). In this case consumption of all iodine sources to form the reactive iodophosphonium species is crucial - a side reaction occurs due to formation of an iodonium species by attack of free iodine on the vinyl group. This is followed by attack of the hydroxyl to form a 6-*exo*-tet cyclisation product, the tetrahydropyran (**262**). Whilst obviously the formation of tetrahydropyran side product **262** is not desired, this reaction provided the first evidence that both the vinyl and hydroxymethyl substituents on the decalin are indeed axially disposed as was thought.



Scheme 2.48 Formation of iodide 260 and tetrahydropyran 262.

Attempts to access desired oxazole **137** by means of displacement reactions of **260** were unsuccessful. Under the same conditions as applied in the tosylate or triflate cases, the iodide undergoes elimination to the bis(alkene) **250**, with recovery of some starting material.

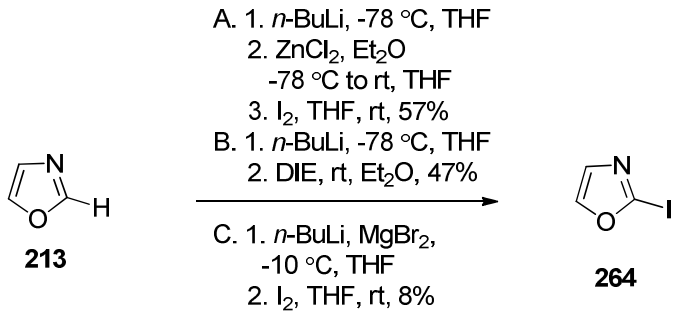
Having formed the iodide **260** we envisaged that the use of an oxazole Grignard coupling with (**263**) to access oxazole derivative **137** would be our next attempt (Scheme 2.49). This 10th generation approach necessitates formation of 2-iodooxazole (**264**), which should be accessible from the parent oxazole **213**. Generation of the corresponding oxazole Grignard regent and coupling with iodide **260** would provide desired substrate for IMDA as envisaged in previous approaches.



Scheme 2.49 10th Generation approach *via* Grignard coupling of iodide 260.

Copper (I) catalysed cross-coupling between Grignard reagents and alkyl bromides as reported by Kochi and Tamura[93] was the main literature precedent which inspired the above approach. Interesting results on the deprotonation of oxazoles and their reactivity towards electrophiles were reported by Mongin *et al.*[94,95] The deprotonation of the oxazole using 1/3 equiv. of a magnesiated species (Bu_3MgLi) generated *in situ* can be achieved by reaction of *n*-BuLi and magnesium bromide, then trapping the metallated oxazole with molecular iodine was reported to give 2-ioodooxazole **264** in 70% yield (Scheme 2.50). Putting this methodology in to practice we found the product formed in a yield as low as 8%. Precomplexation of oxazole with borane[86] before deprotonation and quench with the electrophile gave iodide **261** in low yields also.

Greaney *et al.* used 1,2-diiodoethane and LHMDS to access 2-iodo-4,5-disubstitured oxazoles.[96] Application of this methodology exactly as reported was not successful, but a change of base to *n*-BuLi gave **261** in moderate 47% yield (Scheme 2.50).

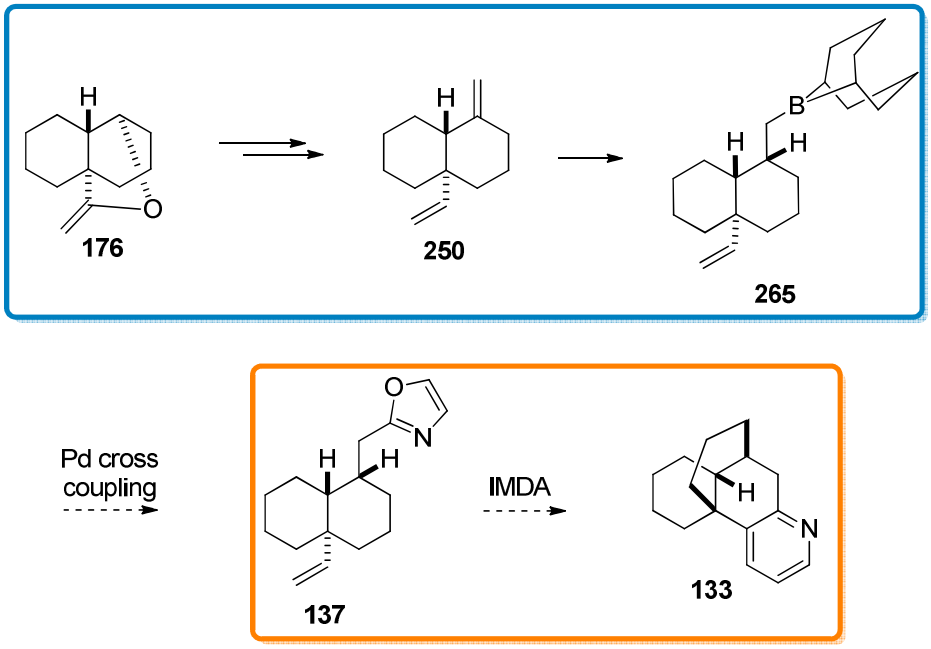


Scheme 2.50 Formation of 2-iodooxazole 264.

Following a procedure from the patent literature[97] procedure, lithiated oxazole was transmetalated with zinc before adding iodine to the reaction mixture. Our best results gave 57% of the iodo product in comparison to the literature reported yield of 69%. Reaction using borane–THF complex did not offer any improvement, yielding the iodooxazole in a lower 19% yield.

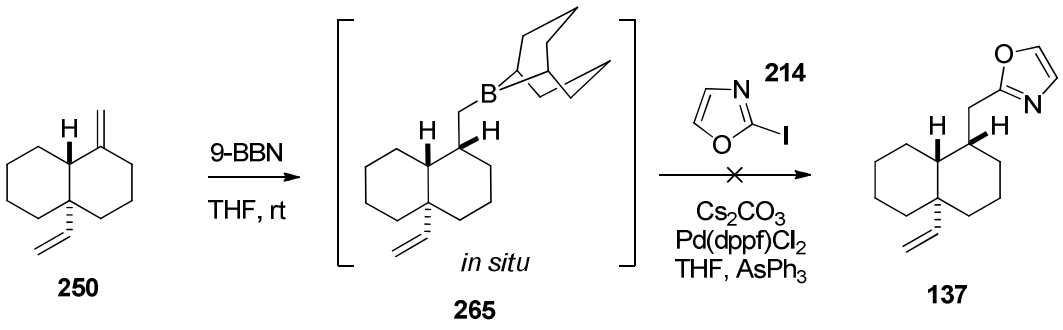
With 2-iodooxazole in hand, we attempted the copper (I) catalysed cross-coupling between oxazolemagnesium iodide (**263**) and iodide **260**. In every instance, no desired product was obtained. As the stability of 2-iodooxazole was marginal, we employed protocols wherein this reagent was used immediately upon generation. These were equally fruitless, however.

Returning to the hydroboration of the alkene **250** in order to access the one-carbon homologated alcohol **249**, this two-step procedure initially involves formation of the borane (**265**), which is subsequently oxidised with base and hydrogen peroxide. The possibility was entertained that a palladium mediated cross-coupling employing the borane **265** with the iodooxazole **214** might allow access to the desired IMDA substrate **137**. This 11th generation approach is detailed in Scheme 2.51.



Scheme 2.51 11th Generation approach *via* Pd mediated cross coupling of borane 265.

The reaction of alkylborane derivatives with halides is a useful tool when it comes to alkene substrates. Typically 9-BBN is used in cases of terminal alkenes. This procedure has been used widely in synthesis of steroids[98,99] or other natural products.[100-103] Suzuki coupling of borane **265** with 2-iodooxazole was tested (Scheme 2.52).



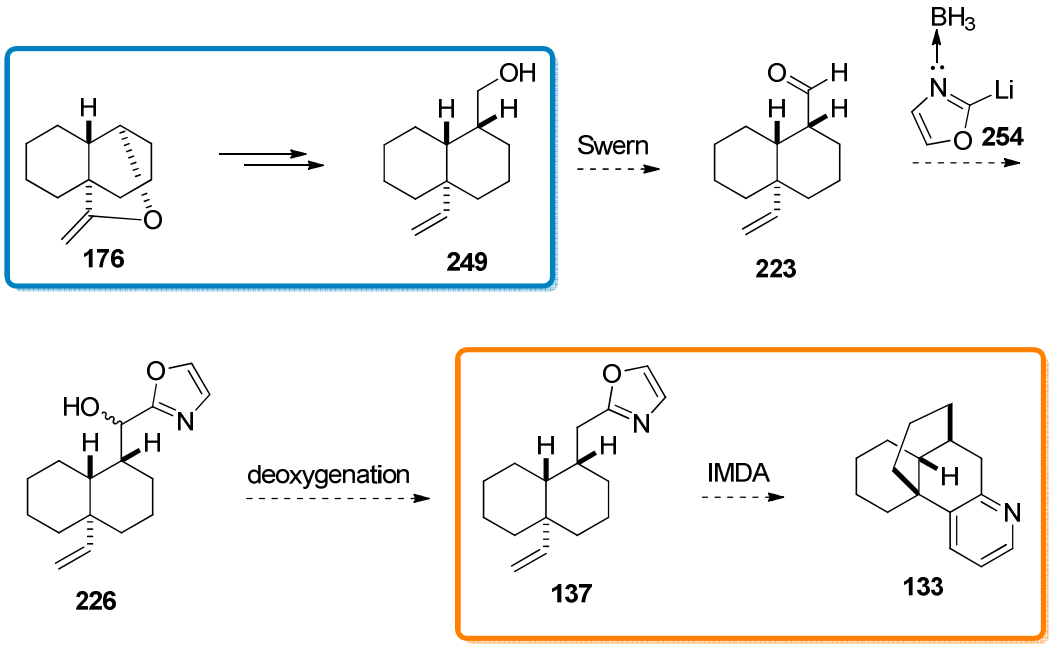
Scheme 2.52 Formation of borane 265 and attempted Suzuki coupling.

Pd(dppf) (II) chloride and Cs_2CO_3 as base are the most commonly used conditions for this type of reaction. When borane **265** was treated *in situ* with these reagents, no formation of the desired product was observed. Use of other

bases or additives such as triphenylarsine did not make any difference to the course of the reaction. In all cases bis(alkene) **250** was recovered. It is most likely that β-hydride elimination occurred after oxidative insertion of palladium into the carbon-boron bond. We sought to examine briefly the use of other boranes, but bis(alkene) **250** was inert to hydroboration with catecholborane.

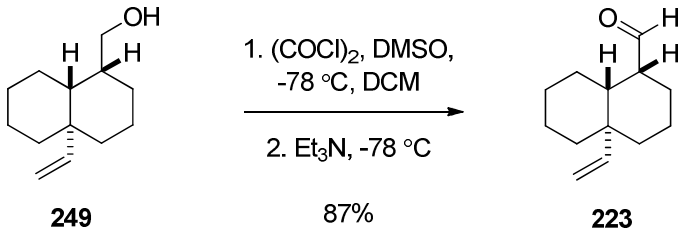
2.2.6 Reaction of lithiated oxazole-borane complex with aldehyde

The borane oxazole complexation methodology described above allowed us to consider new synthetic strategies. We conceived a new approach, which was to proceed by oxidation of the alcohol **249** to the corresponding aldehyde **223**. Then the aldehyde would react with the lithiated oxazole-borane complex **254** in accordance with Vedejs' protocol.[86] Successful formation the 2-oxazolyl alcohol **226** followed by deoxygenation would derive the desired IMDA precursor **137** (Scheme 2.53).



Scheme 2.53 12th Generation approach *via* oxazole reaction with the aldehyde 223.

To access the aldehyde, a Swern oxidation was very successful, giving the aldehyde **223** in 87% yield as a single diastereomer, i.e. with negligible epimerisation at the aldehyde α-position (Scheme 2.54).



249 87% **223**

Scheme 2.54 Swern oxidation of the alcohol 249.

The relative configuration of the vinyl aldehyde **223** was elucidated based on a NOESY correlation between the aldehyde proton and the vinyl -C*H*=CH_2 proton (Figure 7), which indicated that the vinyl and aldehyde groups are located on the same face of the *trans*-decalin skeleton (i.e. both are oriented axially, Figure 2.4). This provided compelling evidence that the configuration we had inferred for the new stereocentre in hydroboration product **249** was correct.

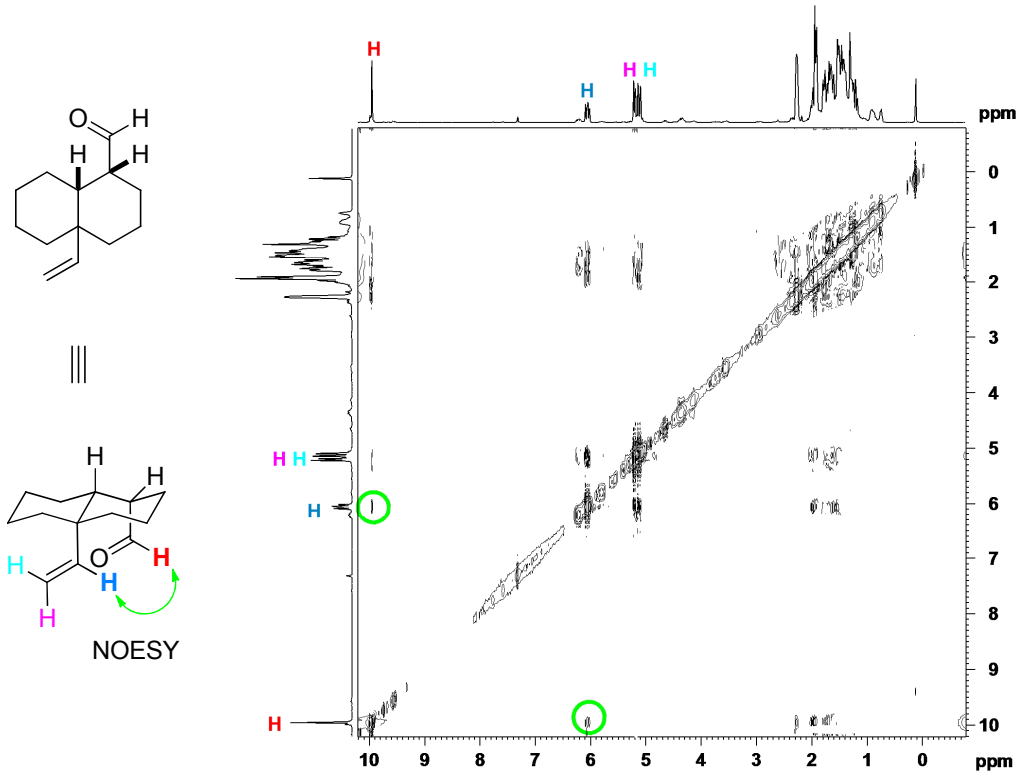
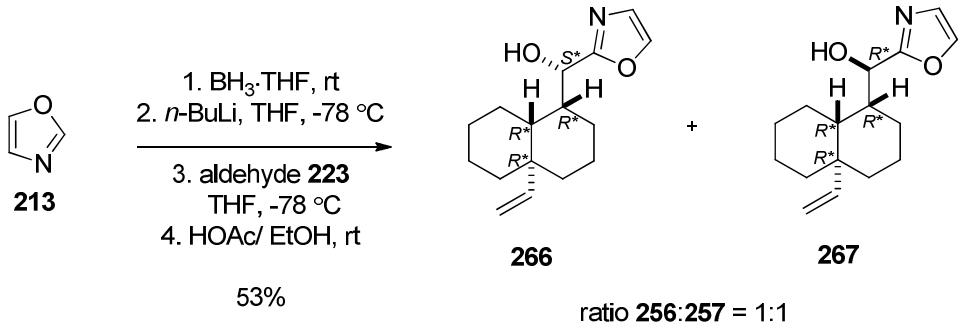


Figure 2.4 NOESY correlations for vinyl aldehyde 223.

Treatment of oxazole **213** with borane, followed by lithiation and addition to aldehyde **223** using Vedejs' protocol afforded the desired product as a mixture of two diastereomers (**266**) and (**267**) in 53% yield (Scheme 2.55).



Scheme 2.55 Reaction of the aldehyde 223 with an oxazole using Vedejs protocol.

No substrate control of stereochemistry was observed; the ratio of the diastereomeric products was 1:1. These proved to be separable by careful column chromatography. The configuration of the newly formed stereocentre was deemed unimportant, since after deoxygenation a single isomer would once again be obtained.

The relative configuration of one of the diastereomers, **266**, was determined by X-ray crystallography (Figure 2.5).

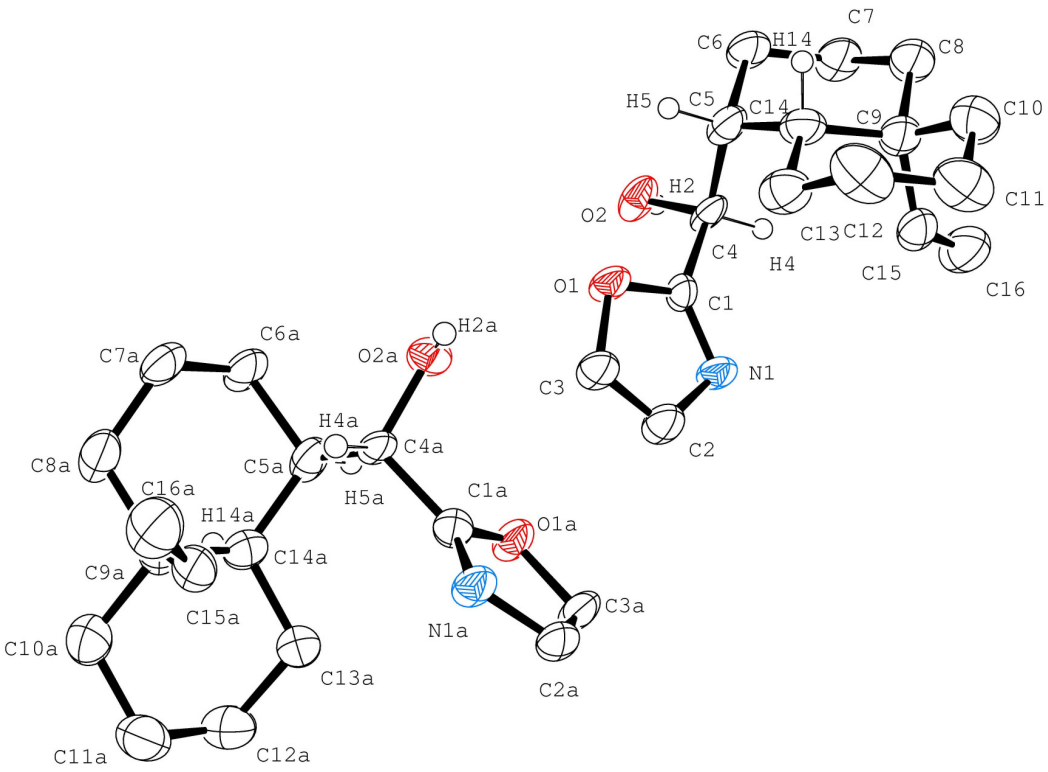


Figure 2.5 Crystal structure for 266, showing two discrete molecules in the unit cell. Ellipsoids at 50% probability. Selected H atoms are shown as spheres of arbitrary radius and a disordered molecule of chloroform solvent has been omitted for clarity.

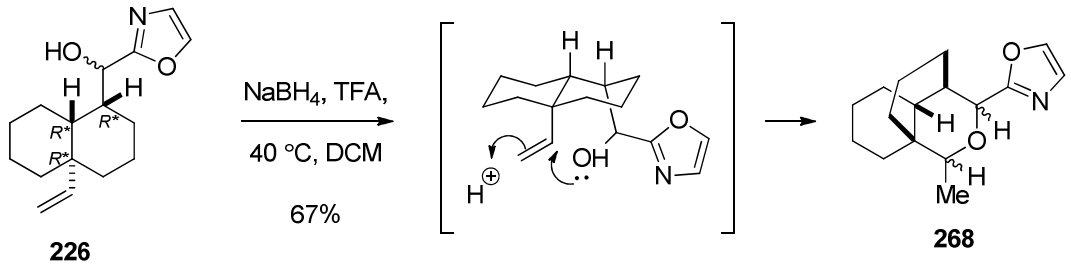
The low yield of the reaction is due in part to the competing action of borane as reductant, reducing the aldehyde to the corresponding alcohol **249**. This was observed in every instance, with **249** being isolated in an average yield of 45%. Other boron Lewis acids were used to avoid the reduction occurring. Intriguingly

none of these were useful in terms of improvement of reaction yield. Triethylborane provided some of the product alongside some of the starting material and other degradation products. Use of boron trifluoride etherate was even less successful; no desired product formation was observed, nor was starting material recovered.

2.2.7 Attempts at deoxygenation

The next step towards completion of the proposed model system would involve deoxygenation of the alcohols **226**.

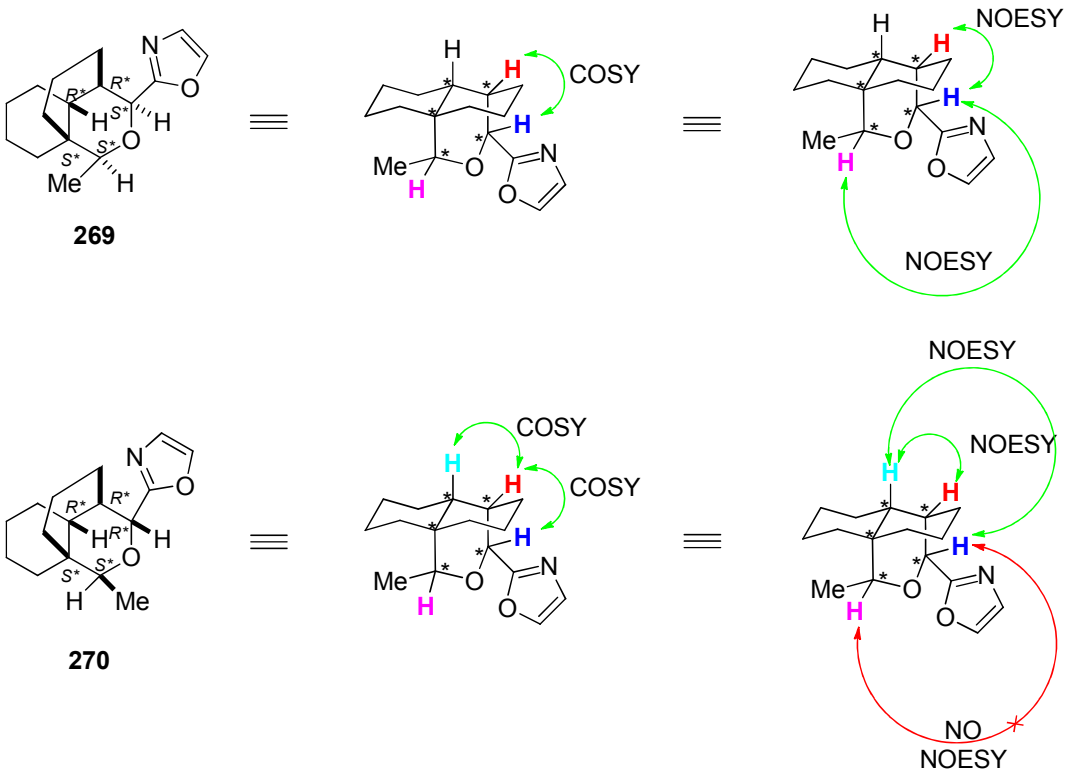
There is only sparse literature precedent for dehydroxylation at the α-position of a heterocyclic fragment. In our initial attempts to reduce the 2-oxazolyl alcohols **226**, we employed the procedure of Nutaitis and Swartz for the reduction of heterocyclic secondary α-carbinols.[104] The procedure is a modification of that developed by Gribble *et al*.[105] – reduction with sodium borohydride and TFA is reportedly effective for the synthesis of diaryl or hetaryl-aryl methanes. We subjected a mixture of diastereomeric alcohols **226** to the reported conditions. The reaction went to the completion after 3 h, but afforded unexpected products (Scheme 2.56).



226 **268**

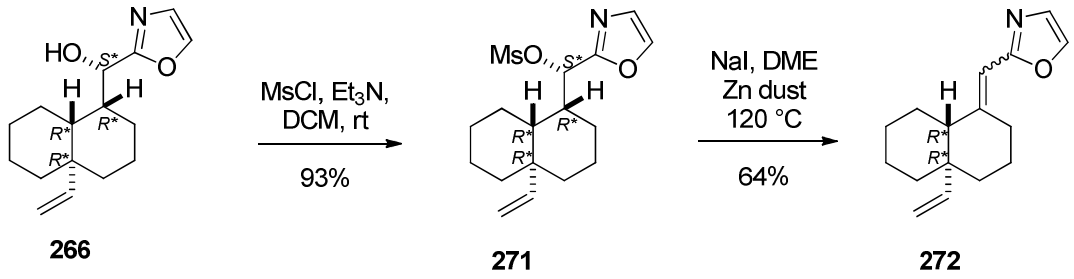
Scheme 2.56 Attempted reduction of 2-oxazolyl alcohol 226 using Gribble and Nutaitis' conditions.

The formation of the observed diastereomeric mixture of tricyclic tetrahydropyrans (**268**) is easily rationalised. TFA effected protonation of the vinyl group and the resultant carbocation was attacked by the hydroxyl oxygen to yield the cyclisation product **268** after loss of a proton. The reaction did not furnish the desired deoxygenated product **137**, but formation of byproduct **268** allowed the relative configuration of **249** to be inferred: for **268** to form requires a particular stereochemistry in the starting molecule **226**, that shown in Scheme 2.56. As alcohol substrate **226** was used as a mixture of 2 diastereomers, the product **268** was formed as all four possible diastereomers. We successfully separated and assigned the configurations of two of these diastereomeric tetrahydropyrans. The relative configuration of the two products was established by COSY and NOESY correlations (Scheme 2.57). See appendix for NMR spectra.



Scheme 2.57 Correlations of COSY and NOESY for identified products 269 and 270.

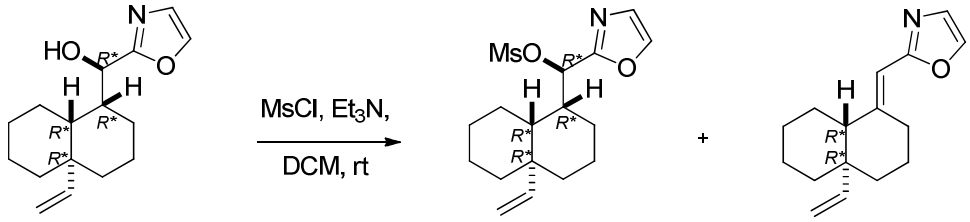
An alternative dehydroxylation methodology is that reported by Barenjee *et al.*, who successfully deoxygenated aromatic secondary α-carbinols by reduction of the corresponding tosylate with sodium iodide and elemental zinc.[106] The application of this methodology required mesylate (**271**), which was accessed from alcohol **266** in 93% yield (Scheme 2.58).



266 **271** **272**

Scheme 2.58 Mesylation of alcohol 266 and attempts at reduction.

Attempts to reduce mesylate **271** did not give the desired deoxygenated compound; rather, they afforded the elimination product (**272**) as a single isomer (Scheme 2.59)

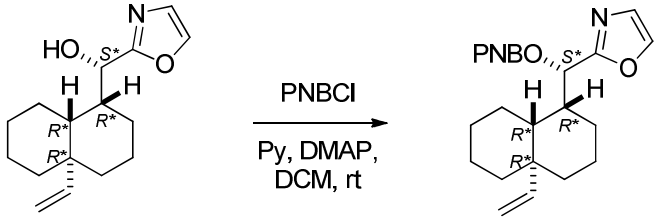


267 **273**, 81% **272**, 18%

Scheme 2.59 Mesylation of alcohol 267.

The question of whether the elimination occurred from mesylate **266** or from the iodide formed *in situ* is not clear. Possibly relevant to this question is the observation that the other diastereomeric mesylate (**273**) is less stable and undergoes elimination under the conditions of its formation. Thus, it is plausible that mesylate **271** can undergo direct elimination under harsher conditions without the intermediacy of the corresponding iodide.

In order to obtain higher quality x-ray diffraction data for the products of lithiated oxazole-borane complex addition to aldehyde **223**, formation of a derivative was carried out. Thus, the esterification of the vinyl alcohol **266** gave the *p*-nitrobenzoate ester **274** with the intention of obtaining crystals of suitable quality for x-ray diffraction, but no such crystals were ultimately obtained (Scheme 2.60).

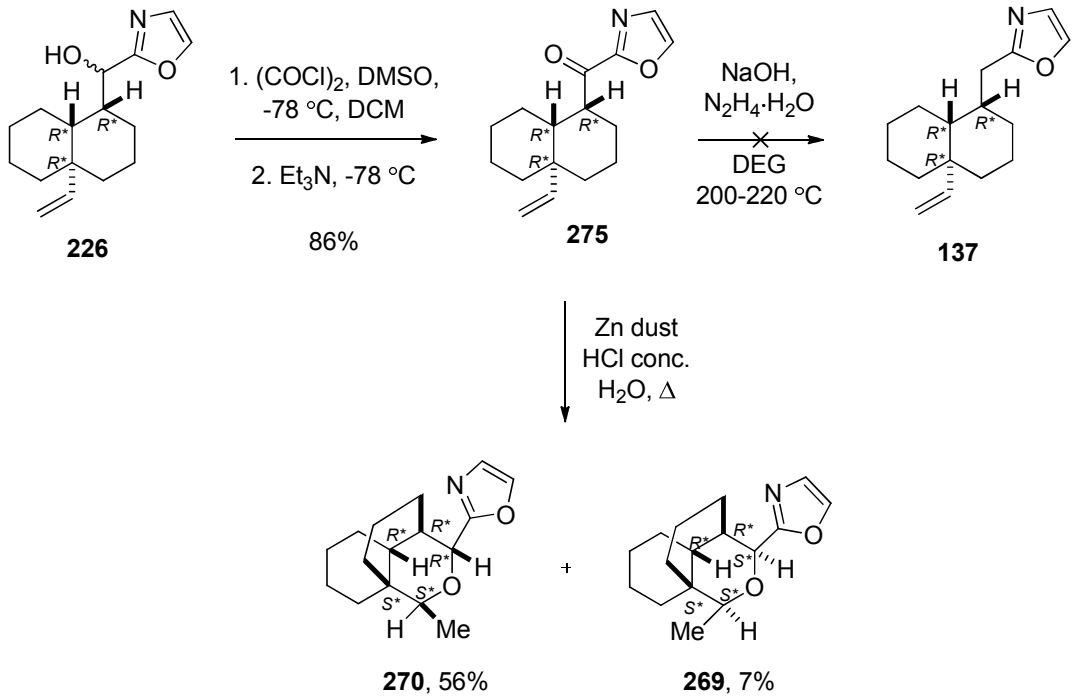


266 **274**

Scheme 2.60 Formation of the PNB ester 274.

Next we attempted to employ a two-step approach comprising oxidation to the ketone and subsequent Wolff–Kishner reduction[107,108]. Additionally, the possibility of reduced product (**137**) undergoing the IMDA reaction *in situ* was considered.

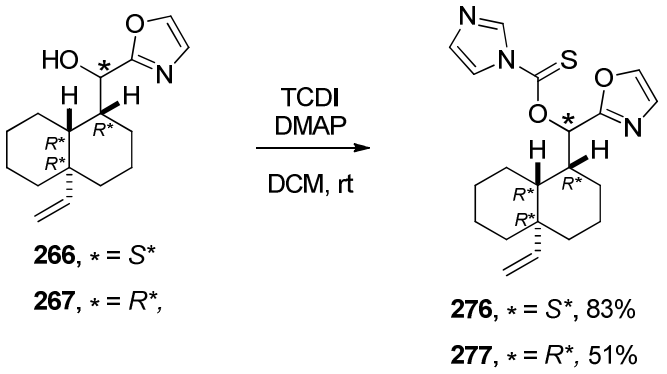
Swern oxidation of the mixture of two diastereomers alcohols **226** provided the ketone **275** in good yield, with no epimerisation occurring (Scheme 2.61). When this was subjected to reduction conditions, the reaction was unsuccessful, leading to complete decomposition of the starting ketone; no hydrazone intermediate was observed either.



Scheme 2.61 Attempted Wolff–Kishner and Clemmensen reductions of ketone 270.

Having ketone **270** in hand, we attempted a Clemmensen reduction[109-111]. This reaction afforded products seen previously. Tetrahydropyrans **269** and **270** formed in 66% yield and in a 1:8 ratio.

Our next approach involved an attempted Barton–McCombie radical dehydroxylation.[112] The required imidazole-1-carbothioate substrates (**276)** and (**277)** were easily accessed from corresponding alcohols **266** and **267** in 83% and 51% yield respectively (Scheme 2.62).



266, * = *S**

267, * = *R**,

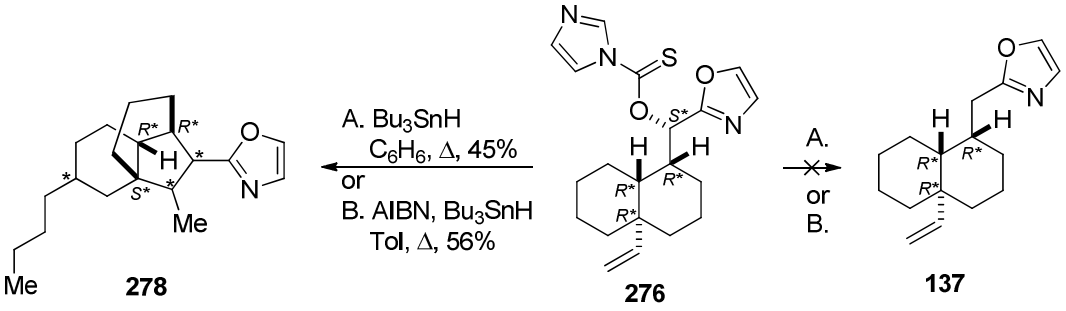
276, * = *S**, 83%

277, * = *R**, 51%

Scheme 2.62 Formation of imidazole-1-carbothioate substrates 276 and 277.

Whilst the Barton–McCombie procedure is typically performed with a sub-stoichiometric amount of AIBN or another radical initiator, there are many literature reports of this reaction succeeding without addition of any radical initiator.[113-115]

In practice, when we attempted this reaction on the substrate **276** at hand, the desired deoxygenated product **137** was not observed. Instead, a byproduct was formed, both in the presence and absence of AIBN (Scheme 2.63).



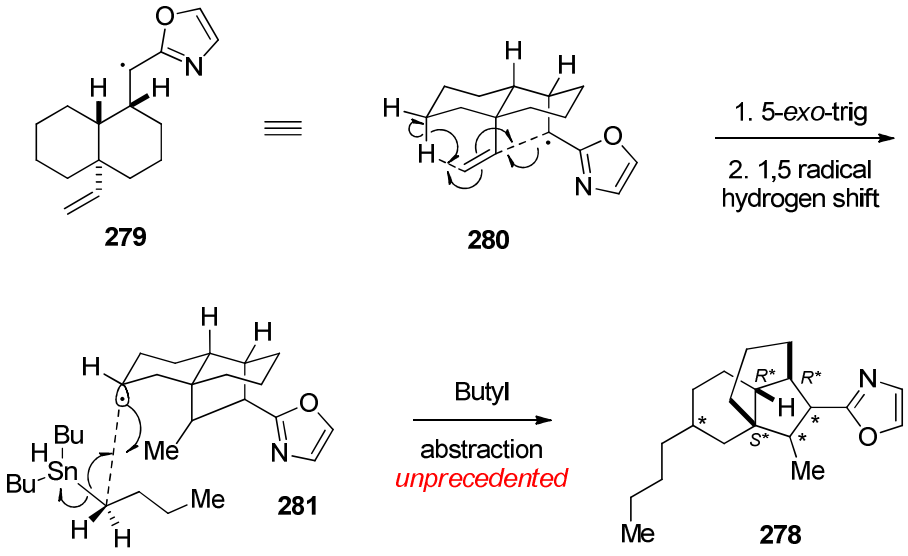
278 **276** **137**

Scheme 2.63 Barton-McCombie reactions on imidazole-1-carbothioate 276.

Although the deoxygenation had occurred to produce (**279**), a radical intermediate appeared to have incorporated a butyl group to give (**278**) (Scheme 2.64). Formation of this product was confirmed by mass spectrometry. Analysis of NMR data showed the butyl -CH_3 triplet peak at (δ = 0.91 ppm) in ^{1}H NMR. There were no vinylic protons present. The ^{13}C-NMR spectrum confirmed

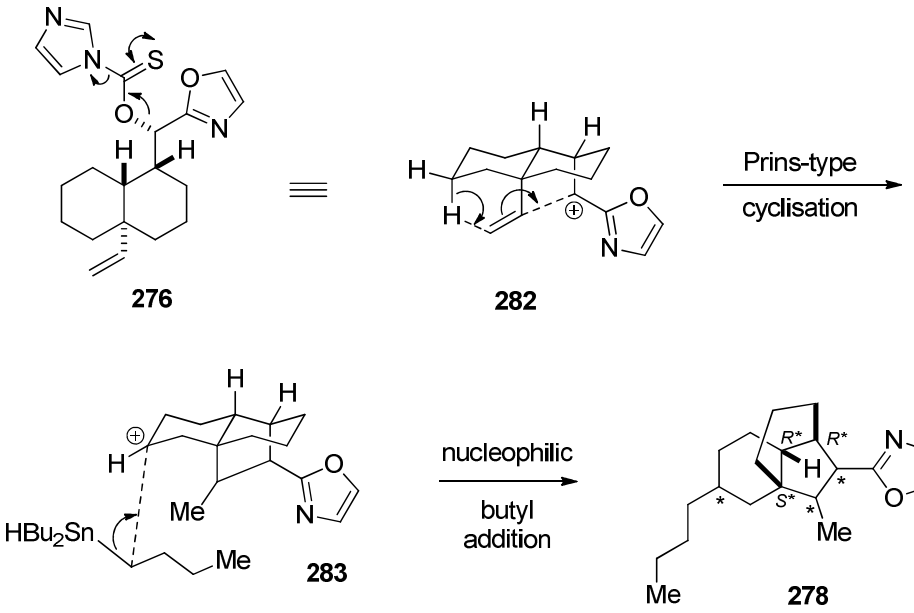
the correct number of carbons were present for the proposed butyl-containing product. Combination of DEPT-135 and DEPT-90 spectroscopic data showed presence of two primary carbons at (δ = 13.5 ppm) and (δ = 11.4 ppm) in the ^{13}C-NMR spectrum.

Our initial mechanistic proposal for this reaction can be seen in (Scheme 2.64). As in a normal Barton–McCombie radical dehydroxylation, a tributyltin radical abstracted the carbothioate group from **276** leaving an alkyl radical **279**. It was then expected that radical **279** would abstract a hydrogen atom from a molecule of tributyltin hydride to give the desired deoxygenation product. However, the presence of an alkene in the molecule and an alignment of reactive groups allowed a 5-*exo*-trig cyclization to occur. Subsequent 1,5 radical hydrogen abstraction, again facilitated by the alignment of reactive groups induced by the *trans*-decalin skeleton, would give alkyl radical (**281**). Whilst such a mechanistic proposal accounts for formation of the tricyclic skeleton, it must necessarily include a radical-mediated butyl transfer from tributyltin hydride as the propagation step.



Scheme 2.64 Possible radical mechanism for formation of butyl incorporation product 278.

To our knowledge, such a radical-mediated butyl transfer from tributyltin hydride is unprecedented in the literature and we therefore formulated an alternative mechanistic hypothesis, proceeding not by radical intermediates, but by a Prins-type pathway. Thus, at elevated temperature, loss of the carbothioate group would lead to formation of a stabilised benzylic cation (**282**). The cation would then undergo a Prins-type cyclisation with concomitant hydride shift to give a cation on the decalin skeleton (**283**). Incorporation of the butyl group would then be by addition of an organometallic nucleophile as opposed to a radical transfer.



Scheme 2.65 Possible ionic mechanism for formation of butyl incorporation product 278.

An interesting anisotropic effect was observed in the ^{1}H-NMR spectrum of **276**. The oxazole *α*-methine resonance was exceedingly deshielded, so much so (δ = 7.07 ppm) that its unambiguous assignment required a COSY spectrum. The relevant COSY correlations can be seen in (Figure 2.6).

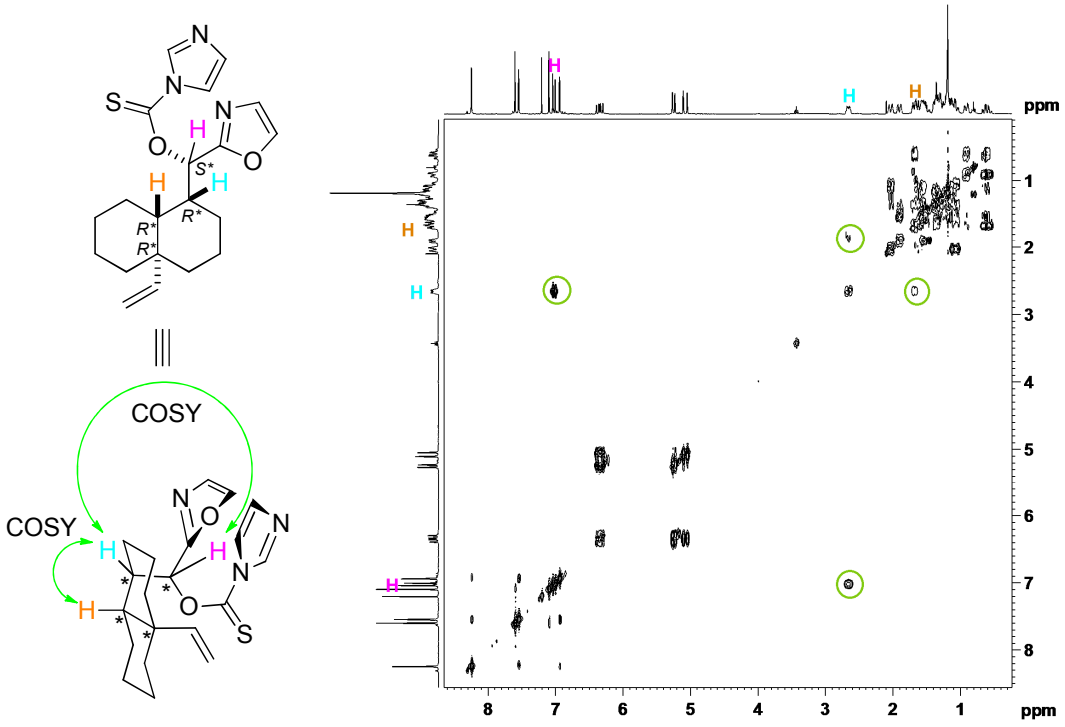


Figure 2.6 COSY correlations for imidazole-1-carbothioate 276.

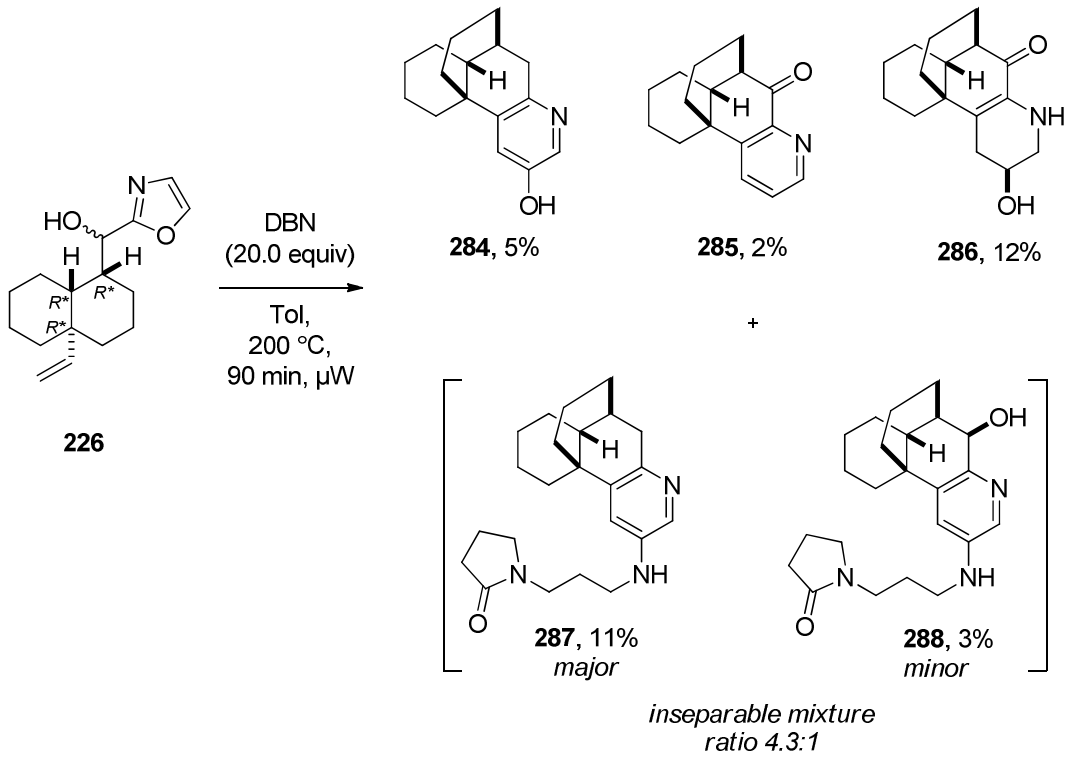
We considered tactics to avoid the unwanted 5-*exo*-trig radical cyclisation onto the alkene and opted temporarily to mask the alkene by functional group interconversion. Attempts to oxidise the vinyl group to the corresponding aldehyde were not successful. Reactions such as ozonolysis did not give product, but completely destroyed the imidazole-1-carbothioate **276** in 15 min. Lemieux–Johnson oxidation[116] with OsO_4 and $NaIO_4$ following Danishefsky's procedure[117] or Upjohn[118] dihydroxylation-oxidation with OsO_4, NMO, $PhI(OAc)_2$ following Nicolaou's[119] procedure for oxidative cleavage of olefins were not effective in our case. Some formation of the product was observed by ^{1}H-NMR monitoring of reaction mixtures; however the amounts were very small and did not change when reaction times were increased. When reactions were performed at elevated temperatures, no vinyl imidazole-1-carbothioate **276** survived.

2.2.8 Kondrat'eva oxazole-olefin hetero- Diels–Alder reaction

Fruitless attempts to accesses the dehydroxylated Kondrat'eva oxazole-olefin hetero Diels–Alder reaction precursor **137** led to our attempting the reaction on the hydroxy derivative **226** using 1,5-diazabicyclo[4.3.0]none-5-ene as per the reports of Ohba.[29,33,50,120,121] It should be stressed that far from being a redundant functional group, a hydroxyl group *α*- to the pyridine ring in the desired product would provide a functional handle for the synthesis of the western hemisphere of complanadine B **5** (which possesses a ketone at this position); alternatively the hydroxyl group could simply be removed subsequent to the pyridine formation.

The first attempts at the reaction, refluxing reaction mixtures in *o*-xylene at 145 ºC with 20 equivalents of 1,5-diazabicyclo[4.3.0]none-5-ene were fruitless. Only starting material was recovered. When the reaction temperature was increased to 180 ºC in 1,2-dichlorobenzene and prolonged reaction time, a small degree of product formation could be observed by NMR.

Accordingly, microwave acceleration was considered. After 90 min of microwave irradiation in toluene at 200 ºC, all starting material was consumed. Purification of the crude reaction mixture afforded five identifiable products of the reaction (**284**), (**285**), (**286**) (**287**) and (**288**) (Scheme 2.66).



Scheme 2.66 Microwave assisted IMDA reaction of the 2-oxazolyl alcohols 226.

Success in production of these pyridines proves the viability of this key reaction. It is clear that all five products arise from IMDA reaction of the oxazole and vinyl moieties. However, the precise mechanisms by which these particular products formed was not clear in the first instance. The corresponding PNB derivatives (**289**), (**290**) and (**291**) were synthesised from **284**, **286** and **287** in the hope of synthesising crystalline materials which would be suitable for X-ray analysis, but in the event no suitable crystals were obtained (Figure 2.7).

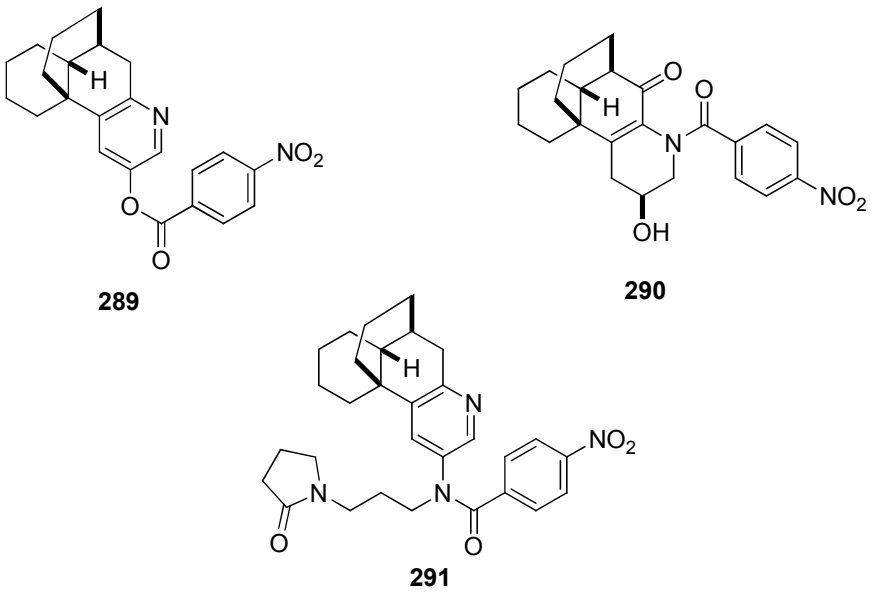
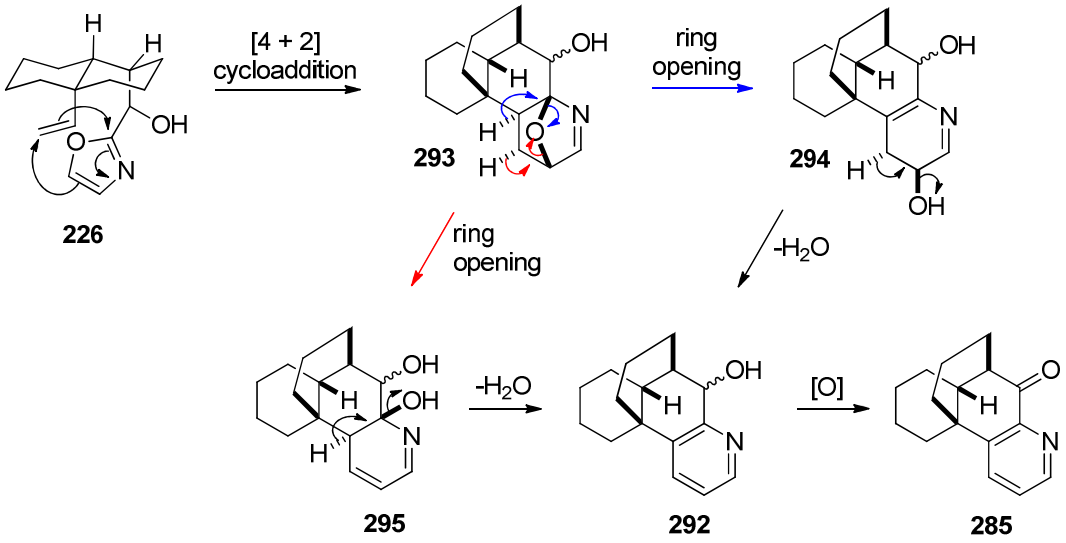


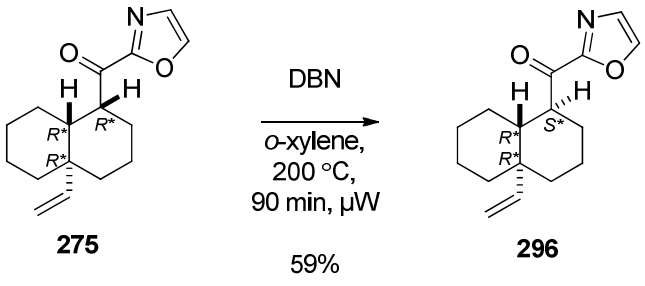
Figure 2.7 PNB derivatives 289, 290, 291.

We propose that pyridyl ketone **285** is formed by oxidation of the corresponding alcohol (the expected product of the reaction) (**292**) and not by oxidation of the reaction substrate **226** (Scheme 2.67). The initial [4+2] cycloaddition provides oxygen bridged adduct (**293**), which undergoes ring opening to give intermediates (**294**) and/ or (**295**). Then these intermediates lose water to furnish the pyridine product **292** and further oxidation gave corresponding ketone **285**.



Scheme 2.67 Mechanism for formation of 285 *via* IMDA of 226.

It is generally the case that electron-withdrawing groups render dienes unreactive towards [4+2] cycloadditions (with the exception of inverse electron demand Diels–Alder reactions). Therefore, an oxazolyl ketone such as **275** would not be expected to be a viable substrate for the direct formation of pyridyl ketone **285**. In practice when ketone **275** was refluxed in *ortho*-xylene with 1,5-diazabicyclo[4.3.0]none-5-ene additive, no cyclization product was observed. Instead the epimerised ketone (**296**) was isolated in 59% yield (Scheme 2.68).



Scheme 2.68 Epimerisation of 275.

We assigned the stereochemsity of the initial cycloadduct on the basis of molecular modelling (MM2 minimisation). On this basis we propose that the initially formed cycloadduct is (**297**) and not (**298**) (Figure 2.8). **297** is lower in

energy than **298** by 25.9 kJ mol^{-1}. It can be seen that for **297**, both decalin rings are able to adopt chair-like conformations, but in **298** one of the decalin rings is appreciably distorted away from the ideal chair geometry due to steric clash with the nitrogen.

297 **298**

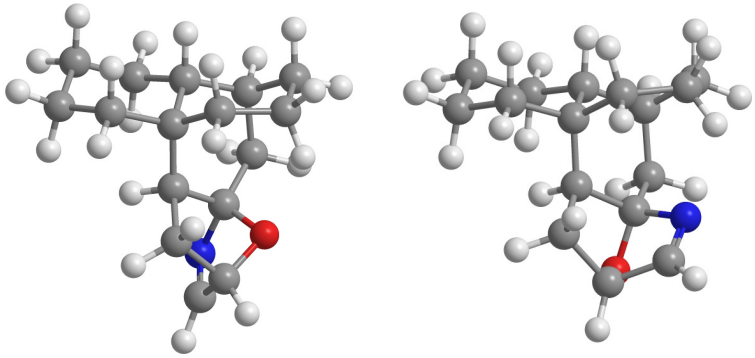
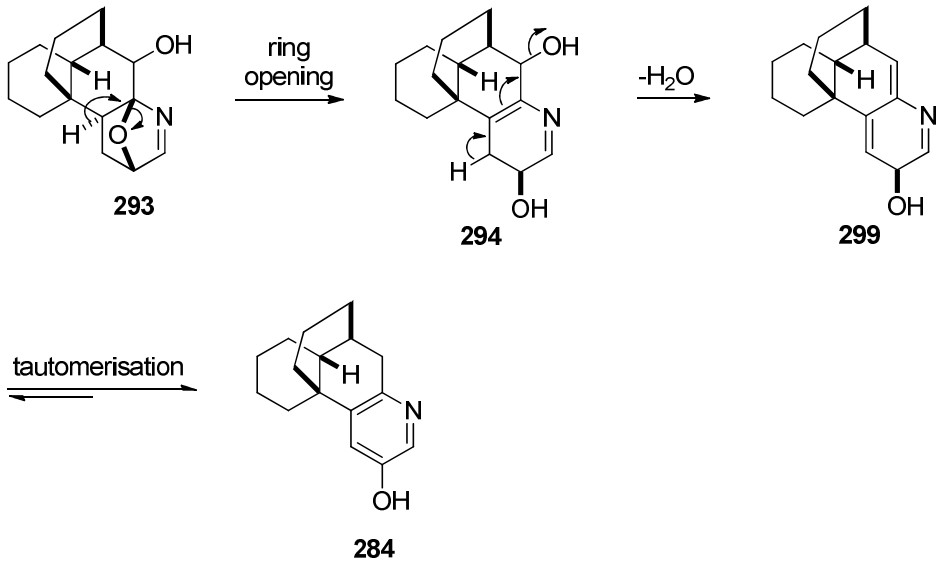


Figure 2.8 Possible cycloadducts and their MM2 minimised structures.

Whereas formation of **284** proceeds *via* a net oxidation reaction, we suggest that products **284, 286**, **287** and **288** are derived from the oxygen bridged cyclisation adduct **293** *via* net redox neutral reactions, as would be expected given the reaction conditions employed.

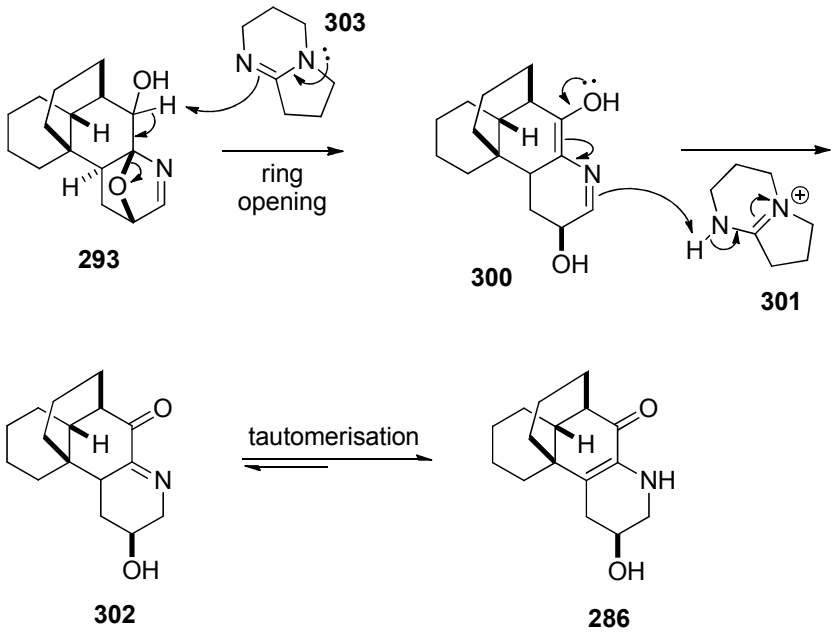
In the case of **284,** after formation of the oxygen bridged intermediate **293**, ring opening gave **294**. Subsequently, we propose that in contrast with the transformation of **294** or **295** to **292** (as per formation of **285**), in this instance an elimination of water occurred *via* the residual aldehyde-derived hydroxyl group to give the intermediate (**299**) (Scheme 2.69). Finally tautomerisation gave the 3-hydroxy pyridine **284** product. We propose the term “diverted Kondrat’eva

reaction" for this transformation; to our knowledge such a formation of a 3-hydroxypyridine is unprecedented in the literature.



Scheme 2.69 Proposed mechanism for formation of 284.

A mechanism for the formation of **286** is proposed in (Scheme 2.70). We suggest the same cycloadduct **293** is the first intermediate. In this instance, the oxazabicyclo[2.2.1]heptene cycloadduct is proposed to fragment by means of the DBN-mediated abstraction of an exocyclic proton, the hydroxyl α-proton, giving the ring-opened intermediate (**300**) and protonated DBN (**301**). Then protonation of the resultant azadienol **300** by **301** provides the intermediate (**302**) which tautomerises to product **286**.

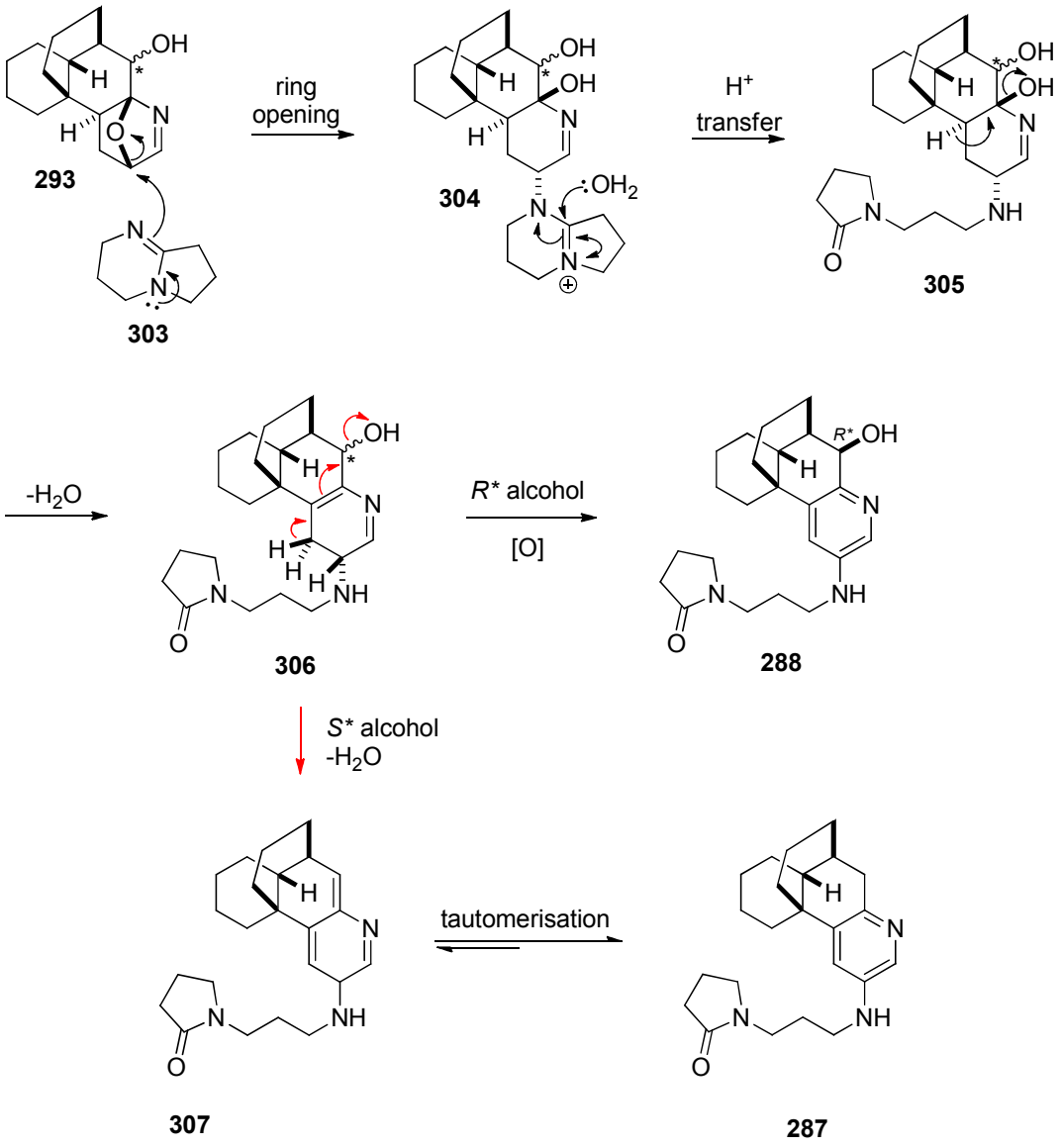


Scheme 2.70 Proposed mechanism for formation of 286.

Finally, for formation of **287** and **288** we propose a more involved mechanism. Starting with the same cycloadduct intermediate **293**, nucleophilic attack of DBN molecule followed by ring opening fragmentation gave (**304**). Water, present in the reaction mixture, attacks the amidinium intermediates **xx1** to form an amide and give ring opened fragment (**305**). Then, elimination of water gives vinylogous alcohol intermediate (**306**). At this instance the two different diastereomers had reacted differently. In the case of *S** alcohol (in the mixture of two in **306**) subsequent elimination of a second water molecule gave (**307**), followed by final tautomerisation to give product **287**. Formation of the minor product must have occurred by oxidation of the *R** alcohol (in the mixture of two in **306**) resulting in direct aromatisation to give the hydroxy product **288**.

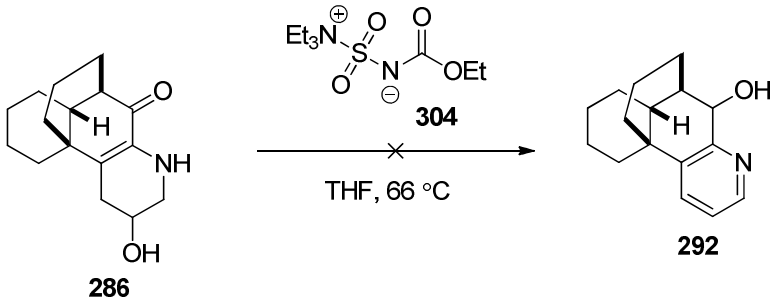
We assign the configuration of **288** as R* alcohol isomer on the basis of the Karplus relationship. We examined molecular models of the two possible diastereomers at the alcohol bearing stereocentre and considered the coupling of the alcohol α-*H* proton with **H** in **288 (**>C**H**-C*H*(OH)<). In the R* isomer, the dihedral angle between these two protons is ≈ 30° which would imply a coupling constant of $J \approx 7.0$ Hz, which is indeed observed. In contrast, the same protons

in the *S** diastereomer, would have a dihedral angle ≈ 90°, which would give rise to a coupling constant of $J \approx 0$ Hz.



Scheme 2.71 Proposed mechanism for formation of 287 and 288.

It was noted that dehydration of **286** would represent an alternative route to the expected pyridine **292**. Attempts at dehydration of **286** with Burgess' reagent[122] (**304**) in order to access the expected product **292** were not successful (Scheme 2.72).



Scheme 2.72 Attemted dehydration reaction of 286 with Burgess' reagent.

Very recently, Mendez *et al.* published the results of theoretical calculations on oxazole cycloadditions with ethylene, facilitated by the addition of an alkyl group, Lewis acid or Brønsted acid to the oxazole nitrogen atom.[123] They found that formation of the oxazolium cation accelerates the reaction rates, making the process more exothermic. Conversely, an oxazole anion has a greater activation energy and renders the reaction endothermic (Figure 2.9). In comparison with neutral oxazole, the cation has a decreased the HOMO–LUMO gap and a more stabilised transition state.

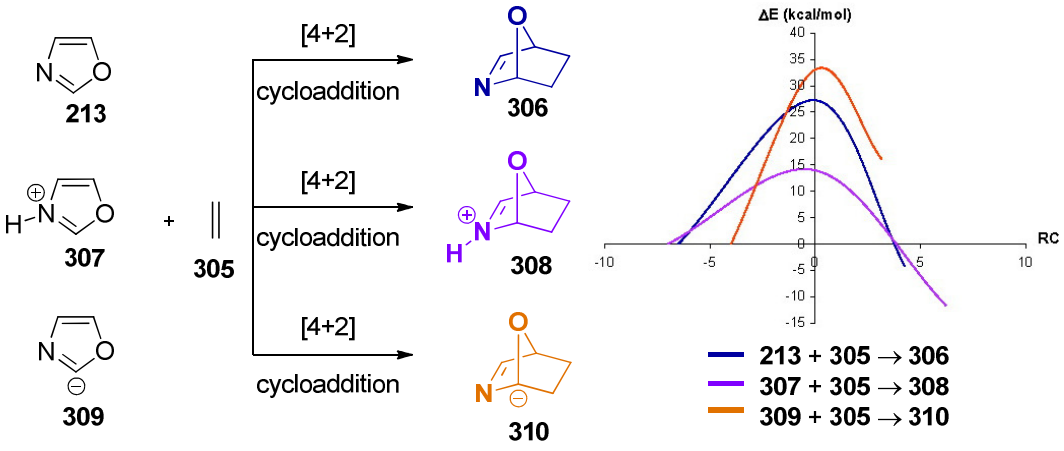
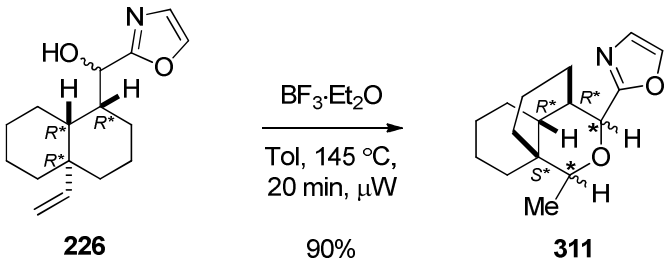


Figure 2.9 Activation energy graphs for neutral oxazole, oxazolium cation and oxazolium anion with ethylene computed at the B3LYP/6-311+G(2d, 2p) level of theory, reproduced from reference 123.

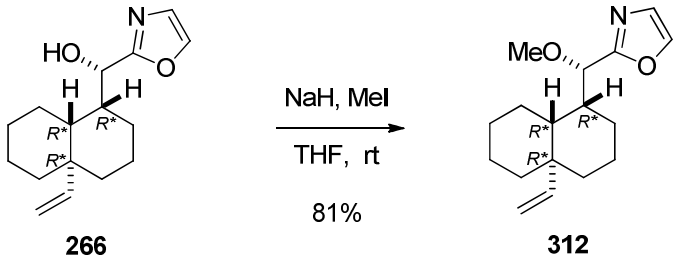
So far, there are no reports in the literature of these theoretical predictions being reduced to practice. In order to ascertain the ability of an oxazolium cation to accelerate the IMDA, we tested reactions of the alcohol **226** with boron trifluoride diethyl etherate as our choice of Lewis acid and acetic acid as our choice of Brønsted acid respectively. Reaction with Lewis acid went to completion after 20 min of irradiation in a microwave reactor at 145 ºC. However, the reaction gave as cyclisation products the tetrahydropyrans (**311**) observed previously when oxazolyl alcohols **226** were treated with Brønsted acid (Scheme 2.73). In this case the product was obtained as all four possible diastereomers in 90% yield; this was a surprising result and is difficult to rationalise mechanistically. A possible explanation could be the presence of trace amounts of hydrofluoric acid in the boron trifluoride diethyl etherate.



226 **311**

Scheme 2.73 Attempted IMDA of 2-oxazolyl alcohol 226 promoted by $BF_3{\cdot}Et_2O$.

In an attempt to prevent this transannular reaction occurring, we thought derivatisation of the hydroxy derivative **266** as the corresponding methyl ether (**312**) might be a solution (Scheme 2.74).



266 **312**

Scheme 2.74 Methylation of alcohol 266.

IMDA on ether **312** using Brønsted acid under microwave conditions were fruitless, furnishing only unreacted starting material. In a reaction of **312** with boron trifluoride diethyl etherate, some pyridine formation was observed by ^{1}H-NMR, however prolonged reaction time lead to decomposition and column purification did not afford any identifiable products.

No further attempts were made to optimise the Kondrat'eva reaction of oxazolyl alcohols **226**. The model system was deemed to have served its primary purpose, namely to demonstrate that the key intramolecular Kondrat'eva reaction is indeed viable. Whilst the unoptimised yields are low, it was not considered worthwhile to attempt to improve on them, since conditions established as being optimal for the model system would not necessarily be applicable in the real system. Efforts towards reaction optimisation would be better directed towards the real system.

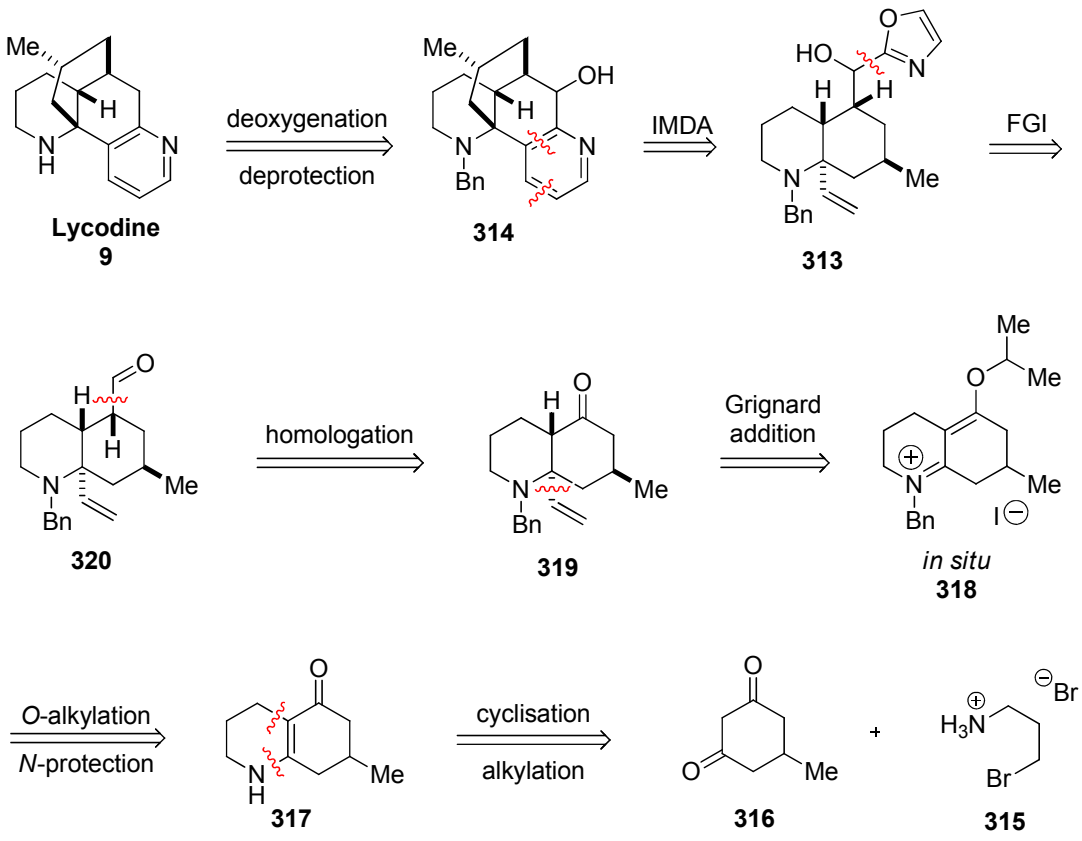
Chapter 3

Results and discussion 2

3. RESULTS AND DISCUSSION II

3.1 Synthetic Results for real system

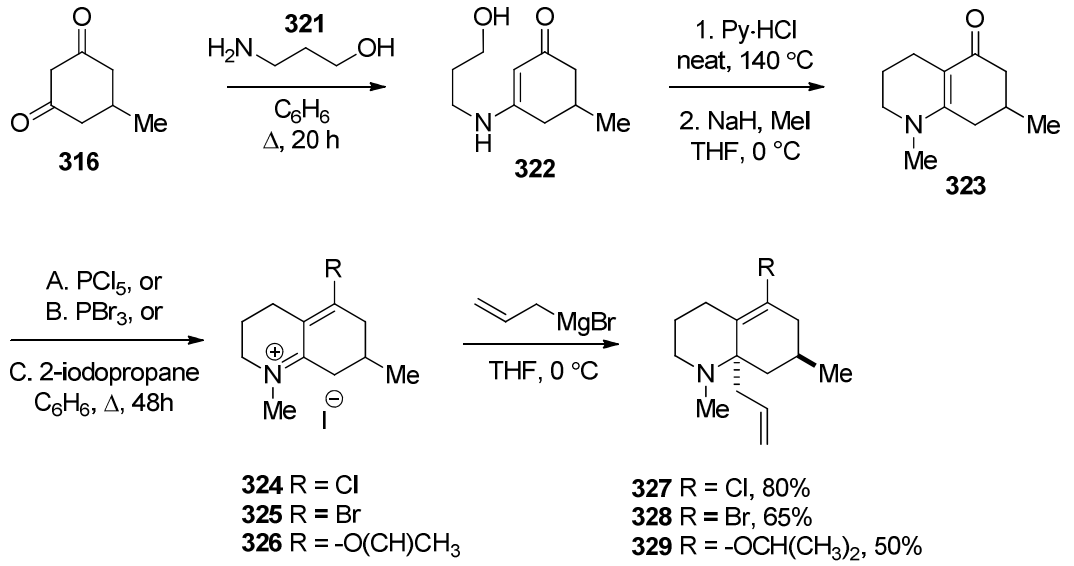
To access the 'monomeric unit' of complanadine A, we envisaged accessing lycodine **9** *via* intramolecular Kondrat'eva oxazole-olefin Diels–Alder reaction of (**313**) followed by deoxygenation and deprotection of the cycloaddition product (**314**) (Scheme 3.1)



Scheme 3.1 Retrosyntheis of lycodine *via* oxazole-olefin IMDA from starting diketone 316. 1st Generation approach.

In the synthesis of IMDA precursor **313** we envisaged employing many steps/ methodologies developed in the model system. We planned to access **313** by reaction of lithiated oxazole-borane complex with aldehyde (**320**). The aldehyde could be accessed by means of an olefination of ketone (**319**), followed by selective hydroboration of the bis(alkene). Subsequent oxidation would produce the one-carbon homologated aldehyde **320**, analogously with the model system. Thus, the precedent established in the model system allows us confidently to disconnect lycodine to a much simpler precursor, azabicyclic vinyl ketone **319.** The early steps employed in the model system would not be applicable to the synthesis of **319**, so a *de novo* route was required. We conceived a route to azabicyclic vinyl ketone **319** that employs methodology developed by Wiesner (*vide infra*). Specifically, **319** should be accessible by means of addition of vinylmagnesium bromide to the salt (**318**) formed by *O*-alkylation of vinylogous amide (**317**). Amide **317** would be protected as the *N*-benzyl derivative and should be readily accessible by reaction of commercially available 3-bromopropylamine hydrobromide (**315**) and 5-methyl-1,3-cyclohexadione (**316**) as reported in the literature.[124]

Wiesner *et al.* attempted to synthesise various lycopodium alkaloids using this strategy of Grignard reagent addition to the salts formed from vinylogous amides.[125-128] In the original publication dating to 1965, Wiesner synthesised vinylogous amide **317** by reaction of diketone **316** and 3-amino-1-propanol (**321**) at reflux in benzene to derive (**322**) (Scheme 3.2).[126]

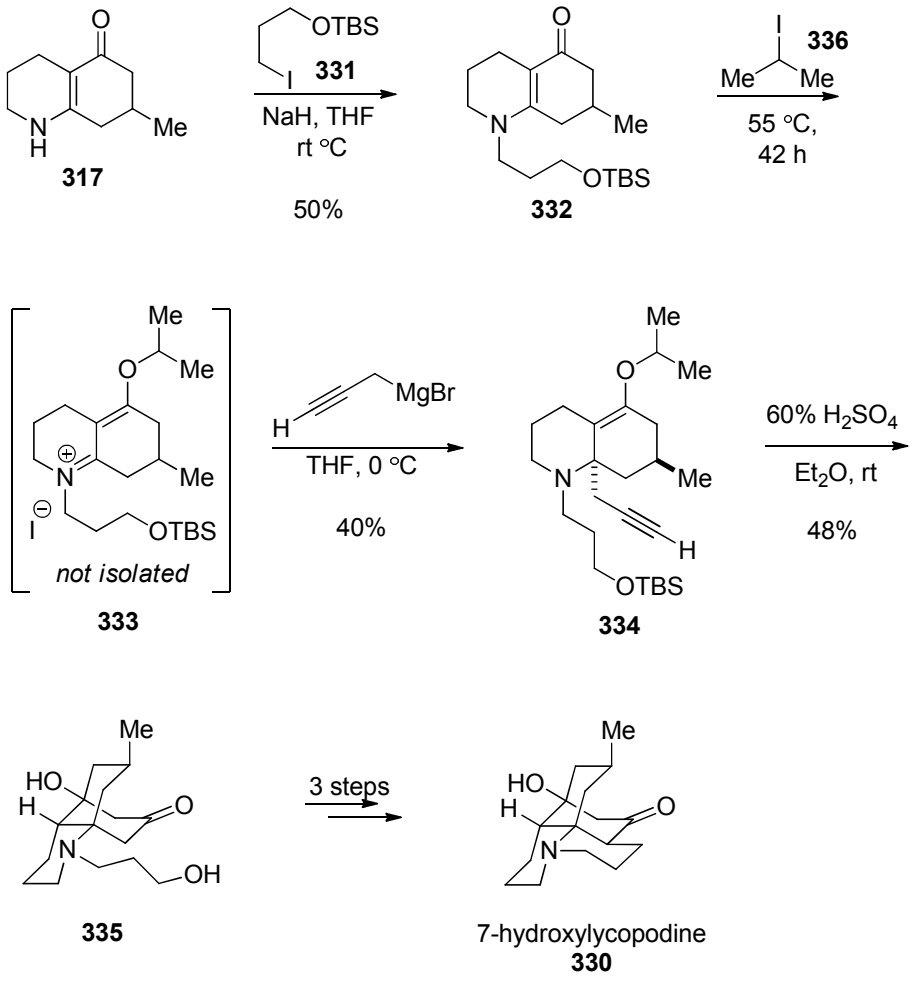


Scheme 3.2 Synthesis of vinylogous amide 323 and addition of allylmagnesium bromide to the salts, as reported by Wiesner[126].

Further cyclisation of **322** in pyridine hydrochloride furnished cyclised vinylogous amide **317** and subsequent alkylation with NaH and MeI gave *N*-methyl derivative (**323**). Further transformations to the corresponding salts were achieved by reacting **323** with PCl_5 to give (**324**), PBr_3 to give (**325**) or reflux with 2-iodopropane in benzene to access (**326**). Reactions of salts **324**, **325** and **326** with an excess of allylmagnesium bromide gave the corresponding addition products (**327**), (**328**) and (**329**) in 80%, 65% and 50% yield respectively (Scheme 3.2). Crucially, the relative configuration of allyl and methyl groups was assigned as *trans*- (by inference from subsequent chemical transformations) and formation of the *cis*-product was observed in a low yield of 3-5% only in the case of **324**. The observed relative stereochemistry is that required for our proposed synthesis.

Much more recently, Snider successfully applied this methodology in the total synthesis of another lycopodium alkaloid, (±)-7-hydroxylycopodine (**330**), providing additional confirmation of the stereoselectivity of the Grignard addition step (Scheme 3.3).[124] Snider used the vinylogous amide **317** in a reaction with (**331**) to give *N*-alkylated product (**332**) which was converted to the salt (**333**)

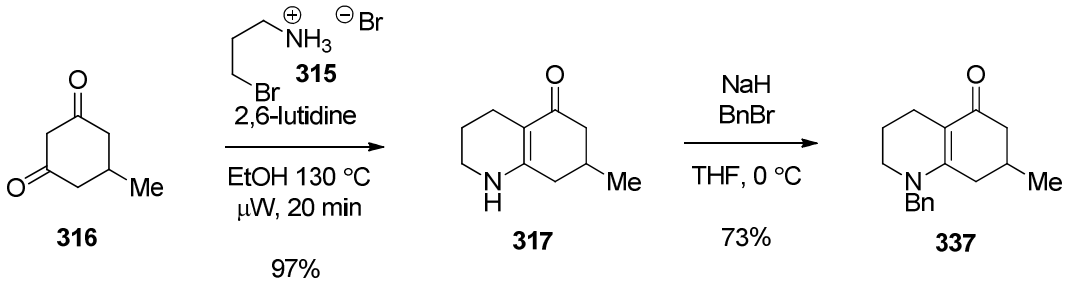
when heated with 2-iodopropane (**336**). The intermediate salt **333** was treated with propargylmagnesium bromide to derive corresponding addition product (**334**). Further Prins cyclisation followed by hydrolysis afforded the tricyclic compound (**335**) which was further elaborated to give the desired alkaloid **330**.



Scheme 3.3 Syntheis of (±)-7-hydroxylycopodine 330 as reported by Snider.

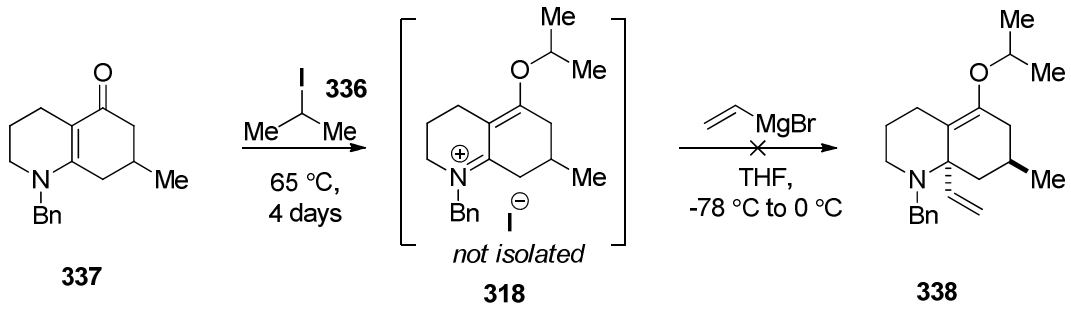
This stereoselective addition of the propargyl moiety suggested the possibility of addition of vinylmagnesium bromide to the salt derived from the *N*-Bn analogue in order to access **319**. We envisaged using benzyl protection as this could be easily cleaved by hydrogenation later in the synthesis.

The forward synthesis began with the formation of the vinylogous amide **317** using microwave assisted conditions as per the reaction conditions reported in Snider's publication.[124] Indeed, this alkylation/annelation reaction between 3-bromopropylamine **315** and dione **316** afforded the vinylogous amide **317** in excellent yield after 20 min of microwave irradiation (Scheme 3.4)



Scheme 3.4 Synthesis of *N*-Bn protected vinylogous amide 337.

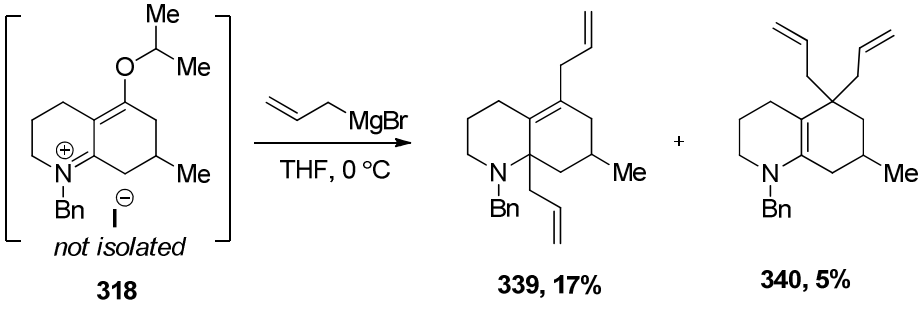
In the protection step the crude vinylogous amide (**337**) was used, affording the corresponding *N*-Bn product in 73% yield (Scheme 3.4). Reaction of *N*-benzylated product **337** with 2-iodopropane at 65 ºC for 4 days in a sealed pressure tube formed salt **318** in quantitative yield (Scheme 3.5). The salt **318** was then immediately dissolved in anhydrous THF and treated with vinylmagnesium bromide at –78 ºC. Unfortunately after workup only the starting *N*-Bn protected vinylogous amide was recovered. A change in the reaction temperature of Grignard reagent addition from –78 ºC to room temperature and even addition to the refluxing solution of the salt in THF did not make any difference, each time unreacted **337** was returned. Neither addition of multiple batches of freshly prepared vinylmagnesium bromide, nor use of vinyllithium was successful.



Scheme 3.5 Salt 318 formation and addition of vinylmagnesium bromide.

Addition of ethynylmagnesium bromide then was considered. In the event of a successful addition, reduction of the alkyne to the corresponding alkene was envisaged to give us the desired vinyl ketone **319** as targeted previously. However, addition of ethynylmagnesium bromide was not successful either, giving only the product of salt hydrolysis, the starting vinylogous amide **337**, as in the previous case.

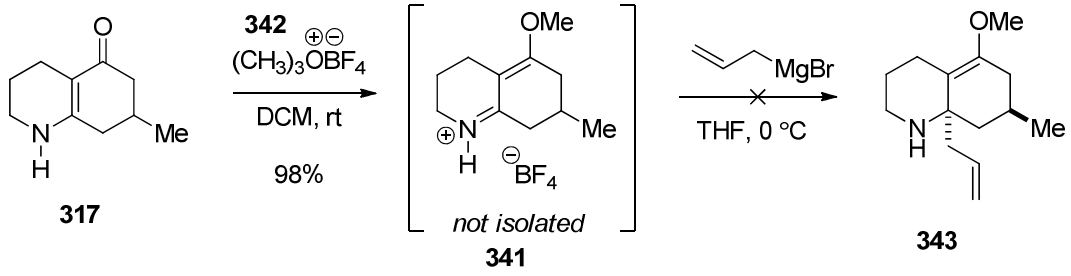
In order to ascertain whether the problem lay in the choice of protecting group or organometallic species, addition of allylmagnesium bromide was tested. Reaction of the salt **318** with excess allyl Grignard reagent led to formation of two double addition products (**339**) and (**340**) in low yield (Scheme 3.6).



Scheme 3.6 Addition of allylmagnesium bromide to the salt 318.

1,4-addition to with respect to nitrogen seems to be favoured, probably due to the steric hindrance caused by the benzyl group rendering access to the desired reactive site *α*- to nitrogen more difficult. In view of these results, we

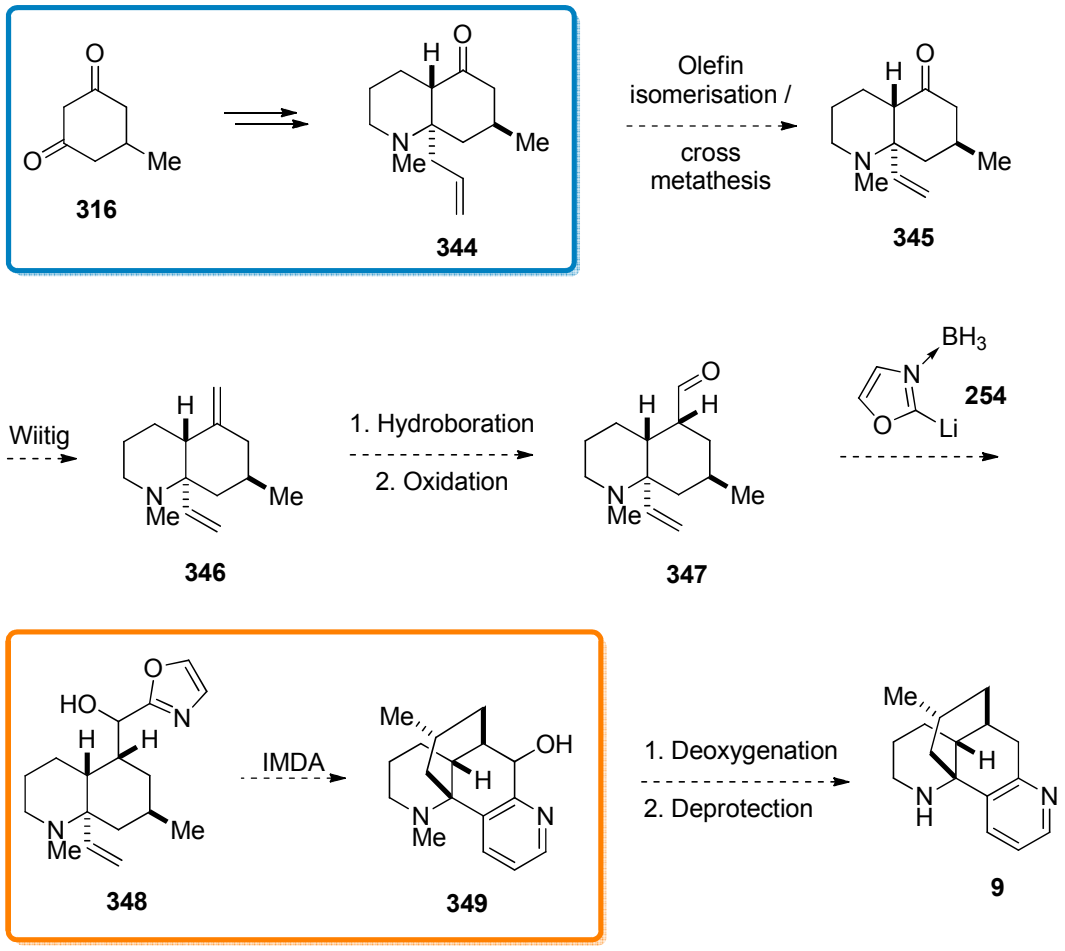
revised the protecting group strategy: next, formation of the 'unprotected' salt (**341**) using Meerwein's salt[129,130] (**342**) was attempted. Reaction with oxophilic trimethyloxonium tetrafluoroborate was performed, which derivered the corresponding salt in 98% yield (Scheme 3.7). Immediate reaction with allylmagnesium bromide in dry THF at 0 ºC gave only the product of salt hydrolysis, the starting vinylogous amide **317**. Most likely, the reason for the unsuccessful addition of the allyl nucleophile to this salt is that the first equivalent of Grignard reagent gave a neutral imine intermediate which is much less reactive towards addition than an imimium species.



Scheme 3.7 Formation of salt 341 with Meerwein's salt and addition of allyl Grignard.

Given that the addition of allylmagnesium bromide to the corresponding *N*-Me salt is reportedly high-yielding[124] we decided to adopt this approach and change our route to *N*-Me protection instead of *N*-Bn. Whilst *N*-methylation is not a common amine protection strategy, we expected that the comparatively unfunctionalised structures of lycodine/complanadine would allow for clean *N*-demethylation post-Kondrat'eva reaction. In a slight modification of our original approach, we envisaged transformation of allyl to vinyl by means of an olefin isomerisation of (**344**), followed by cross-metathesis using Grubbs 2nd generation catalyst[131-133] and ethylene. Successful formation of the vinyl derivative (**345**) would be followed by olefination and hydroboration steps to access (**346**). Further hydroboration step followed by subsequent oxidation to the corresponding aldehyde (**347**) and addition of the lithiated oxazole-borane complex **254** would afford the IMDA precursor (**348**). After a successful [4+2] cycloaddition reaction, (**349**) would then undergo deoxygenation and finally

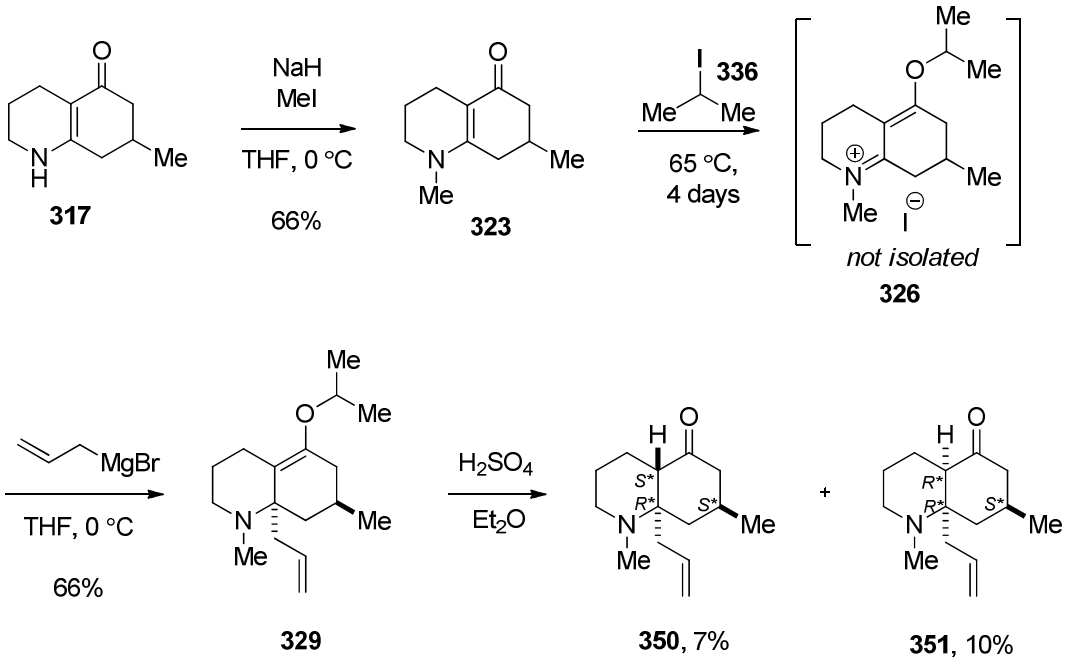
deprotection would derive the target lycodine **9** as planned (Scheme 3.8). Transformations highlighted in blue indicate reactions previously accomplished by Wiesner and Snider.[124] Transformations highlighted in orange indicate our key intramolecular Kondrat'eva oxazole-olefin hetero-Diels–Alder reaction.



Scheme 3.8 2nd Generation approach *via* addition of allylmagnesium bromide to the *N*-Me compound.

Previously prepared vinylogous amide **317** was deprotonated and alkylated with methyl iodide to produce *N*-methylated product **323** in 66% yield (Scheme 3.9). In comparison with the *N*-benzylation, this reaction has proven to be much more challenging to work up and purify due to formation of by-products from impurities from the previous reaction and from undesired *O*-methylation. In

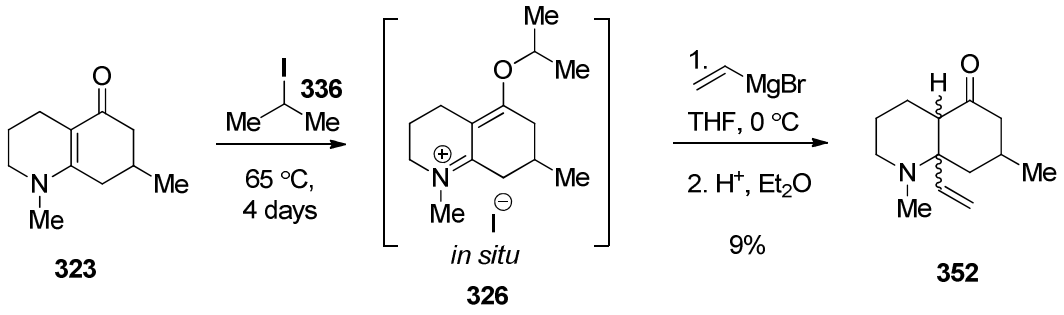
order to obtain a better yield for this reaction, the starting vinylogous amide must instead be purified by column chromatography. After deprotonation with sodium hydride, the alkylating agent must be added very slowly, dropwise to the cooled reaction mixture, to prevent side reactions occurring.



Scheme 3.9 Synthesis of *N*-Me protected vinylogous amide 317 and addition of allyl Grignard to the salt 326.

Having formed the *N*-Me derivative, formation of salt **326** was carried out, giving the product in quantitative yield. Reaction with allylmagnesium bromide yielded the desired addition product in 66% yield from **329** as a single diastereomer (Scheme 3.9) as per the literature procedure of Snider;[124] this is an improved yield with respect to the literature value of the 48%. Hydrolysis of the enol ether **329** with 1 M sulfuric acid in diethyl ether resulted in a mixture of two products (**350**) and (**351**) in total of 17% yield and a diastereomeric ratio of 1:1.4 in favour of the undesired epimer. Unfortunately we were not able to reproduce the yield of 77% and ratio of diastereomers 1:1.7 as published by Snider. Attempts of epimerisation of **351** with 1,5-diazabicyclo[4.3.0]none-5-ene in order to access the desired *trans*-fused azadecalin system were unsuccessful.

At this point a more direct approach which has not been attempted previously was explored: reaction of the salt **326** with vinylmagnesium bromide proceeded to give the desired azabicyclic vinyl ketone, but with no stereoselectivity, resulting in a mixture of two enol ethers, which after hydrolysis afforded an inseparable mixture of 4 diastereomers (**352**) in 9% yield over two steps (Scheme 3.10).

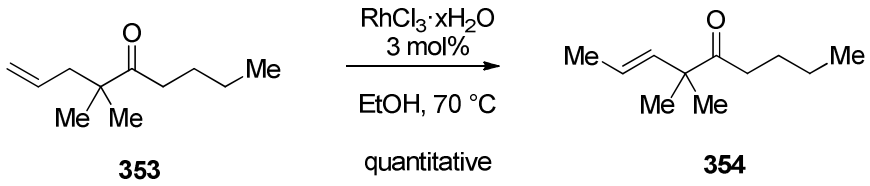


Scheme 3.10 Addition of vinymagnesium bromide to the salt 326.

Attempted addition of ethynylmagnesium bromide to the *N*-Me substrate was also fruitless.

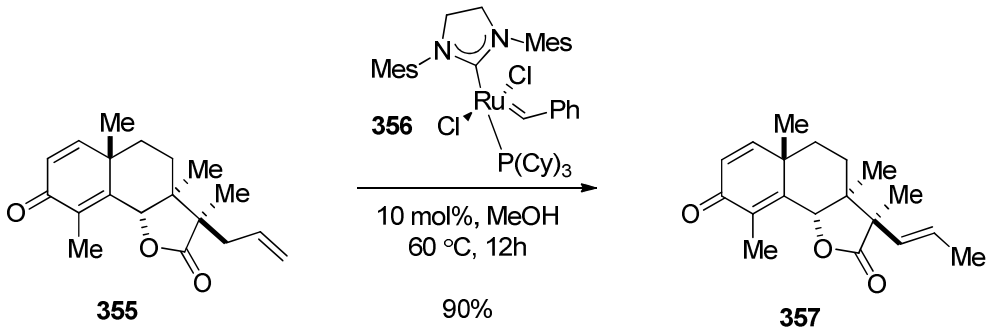
Successful formation of allyl ketone **350** (albeit in low yield) allowed us to explore isomerisation of the allyl moiety and to attempt access to the corresponding vinyl derivative by means of alkene isomerisation.

Probably the most common such isomerisation of alkenes involves the use of $RhCl_3$. In a publication from Nolan, Prunet *et al.*, they employed this reagent to successfully isomerize an allyl fragment appended to a quaternary carbon (**353**) to give the corresponding propenyl derivative (**354**) (Scheme 3.11).[134] Attempts to apply this transformation in our system failed, with only unreacted starting material being recovered.



Scheme 3.11 Isomerisation of 353 using $RhCl_3$.[134]

Hanessian and co-workers published a paper describing isomerisation of unsubstituted terminal *C*-allyl groups to the corresponding 2-propenyl derivatives using Grubbs 2nd generation catalyst (**356**).[135] In this work they demonstrated that a wide range of substrates isomerised in high yields of 75-95% using 10 mol% of the catalyst at reflux in MeOH. An example in Scheme 3.12 shows isomerisation of (**355**) to (**357**), which proceeded smoothly in 90% yield producing the product in a ratio >10:1 *E*/*Z*.

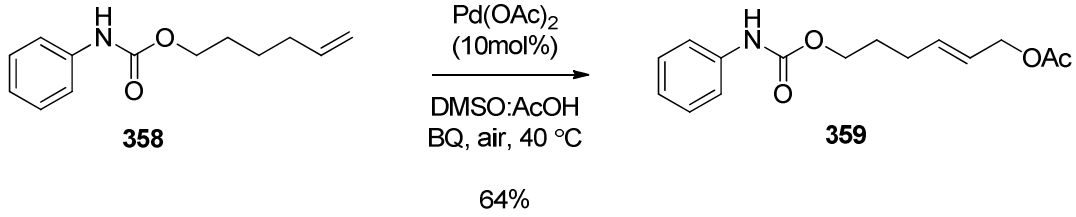


Scheme 3.12 Allyl isomerisation with Grubbs 2nd generation catalyst.[135]

Such methodology appeared attractive in the context of our system, as it raised the possibility of a one-pot isomerisation/ cross metathesis procedure. However, our attempts at this reaction were fruitless. Only unreacted starting material was recovered.

White and co-workers reported methodology to access allylic acetates from monosubstituted olefins.[136-139] This $Pd(OAc)_2$ catalysed allylic C–H oxidation promoted by DMSO or bis(sulfoxide) ligands in acetic acid provides either linear or branched products depending on the reaction conditions. An example of this

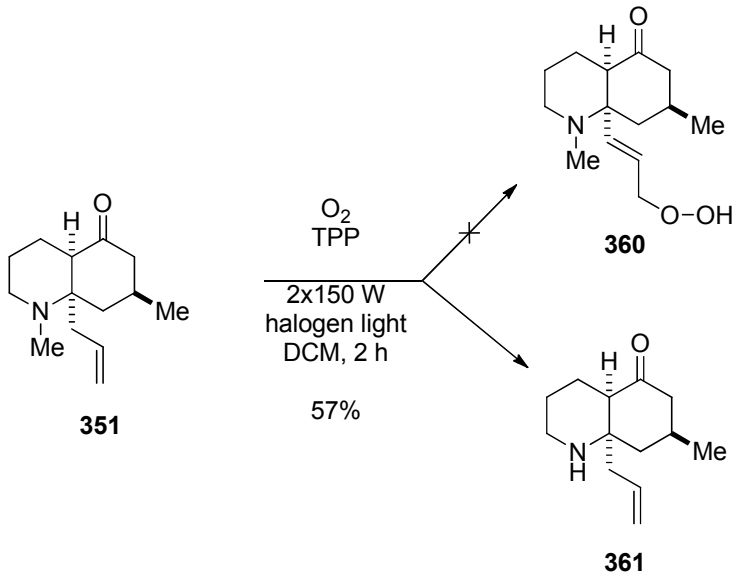
methodology can be seen in (Scheme 3.13). This methodology would allow us to access a double bond migration product.



Scheme 3.13 Allylic oxidation of terminal alkene to allylic acetate by White.[136]

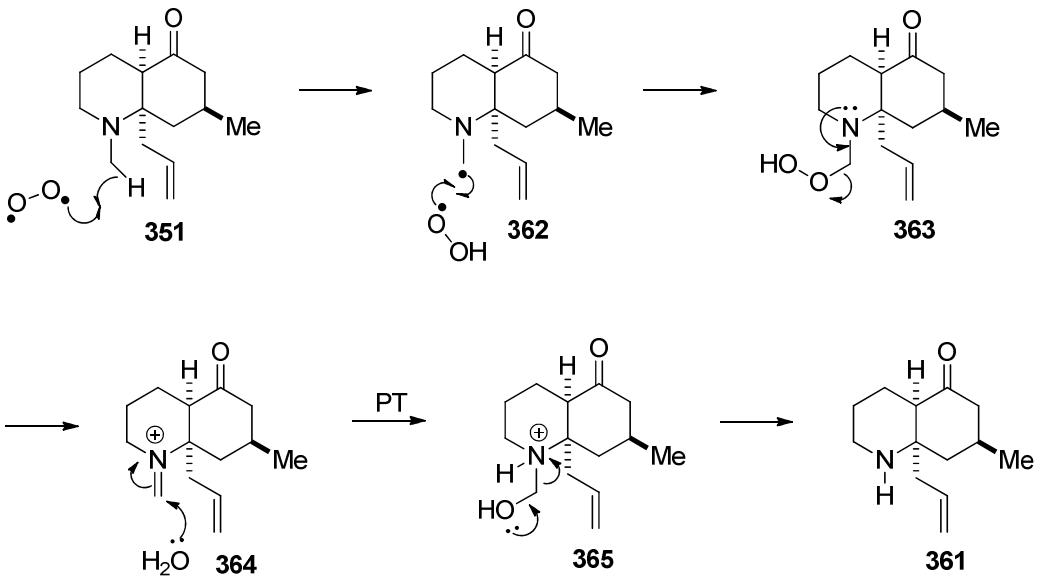
Unfortunately application of this methodology was not successful in the reaction with **350**. Le Bras reported an improvement of this reaction by addition of base,[140] but in our case this was equally unsuccessful.

Olefin migration by means of a Schenk ene reaction[141] was considered next (Scheme 3.14). To access peroxide (**360**), oxygen was bubbled through a mixture of a substrate **351** and photosensitiser (TPP) in MeOH under photoirradiation 2 × 150 W halogen lamps. After 2 h of irradiation, all starting material was consumed as indicated by TLC. Surprisingly, NMR data indicated that the allylic fragment was still present. Of even greater surprise, however, was the absence of the expected *N*-Me singlet peak. After comprehensive characterisation, the product was unambiguously assigned as *N*-demethylated species (**361**), obtained in in 57% yield after column purification.



Scheme 3.14 Attempted ene reaction of 351 with singlet oxygen and *N*-Me deprotection.

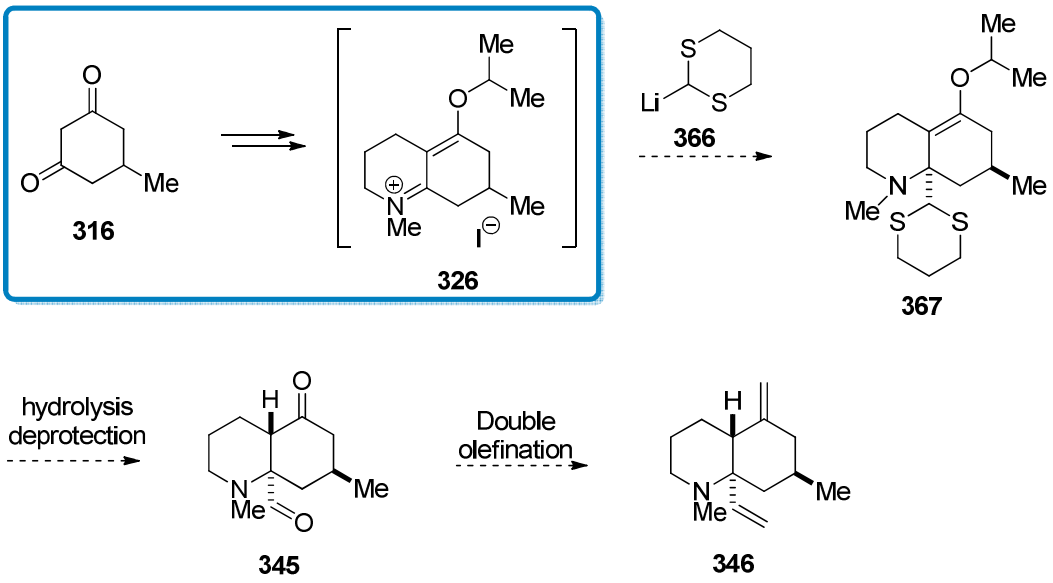
It is not clear what the mechanism for this transformation is. One proposal is shown in Scheme 3.15. Although the intended reaction pathway involved singlet oxygen, it is conceivable that instead triplet oxygen mediates a radical hydrogen abstraction from **351** providing (**362**), which then reacts with peroxide radical to give (**363**). This "perhemiaminal" would be expected to collape to the iminium species, (**364**) which could be hydrolysed during workup to give the deprotected product **361**.



Scheme 3.15 Proposed *N*-Me deprotection mechanism *via* formation and hydrolysis of a "perhemiaminal".

The approaches detailed above constitute the total of our efforts to effect isomerisation of the allyl group; this aim has not been achieved to date.

One further variation on the theme of additions to salt **326** was also considered. The reaction of a lithiated dithiane (**366**) with salt intermediate **326** was explored in order to introduce indirectly the vinyl moiety into the system (Scheme 3.16). If the nucleophile can be successfully added to give the enol ether (**367**), subsequent hydrolysis and deprotection would lead to the formation of dicarbonyl **345**. This could be transformed to the desired bis(alkene) **346** by means of a double olefination. Successful formation of the bis(alkene) would allow us to explore further the synthetic route as envisaged in previous approaches to lycodine.



Scheme 3.16 Approach to the synthesis of the bis(alkene) 346 *via* addition of lithiated dithiane.

In the event, addition of the lithiated dithiane was unsuccessful; only the vinylogous amide **323** was recovered.

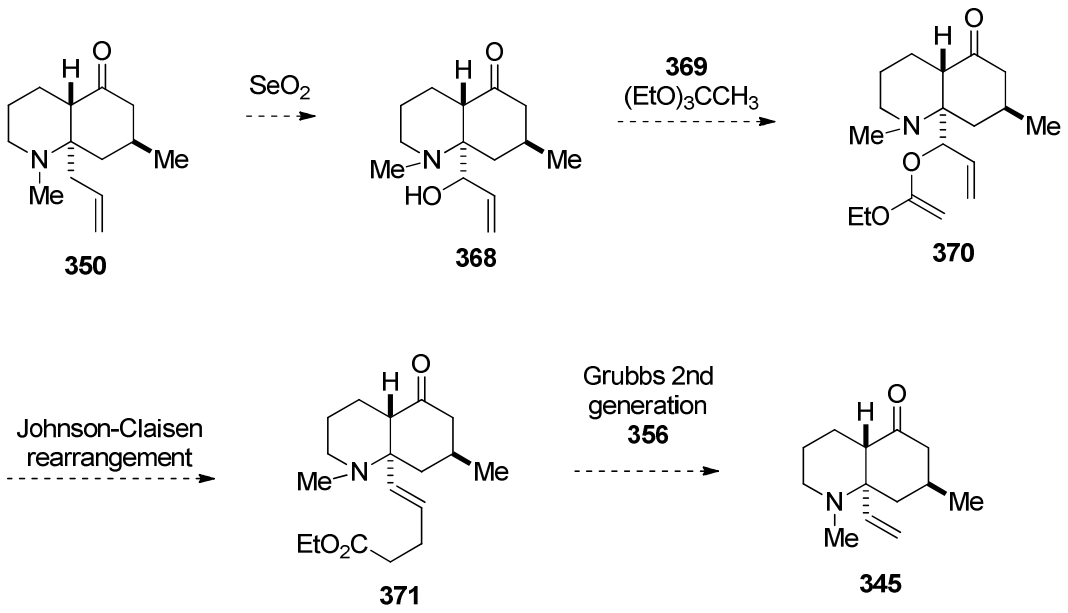
3.2 Conclusions

Formation of the pyridine moiety in our model system validates the intramolecular Kondrat'eva oxazole–olefin hetero-Diels–Alder reaction as a strategy for late-stage assembly of the pyridine ring in a synthesis of lycodine and/or the complanadines. In addition, much of the methodology developed for the assembly of our model system will be of use in the realisation of such a total synthesis.

We have determined that the presence of a hydroxyl group at the *α*-position of a 2-substituted oxazole has the potential to alter significantly the outcome of the Kondrat'eva reaction. This substituent has been shown to be "non-innocent", participating in the cyclisation reaction, e.g. as a leaving group. We anticipate that these findings may be of utility in contexts other than the total synthesis of the complanadines.

3.3 Future work

Work towards synthesis of lycodine and the complanadines could be continued from azabicylic intermediate **350** by attempting alternative approached to effect alkene migration (Scheme 3.17).

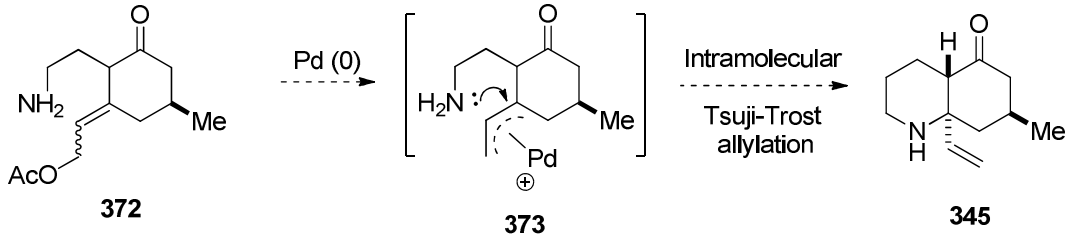


Scheme 3.17 Proposed synthesis of 345 *via* Johnson–Claisen rearrangement.

Selenium dioxide mediated oxidation should provide alcohol (**368**) followed by *O*-alkylation with triethyl orthoacetate (**369**) to give (**370**). Then Johnson–Claisen rearrangement would provide (**371**). Next Grubbs' cross metathesis with ethylene should finally derive vinyl ketone **345** which could be used in further steps as previously envisaged, applying methodology developed in model system.

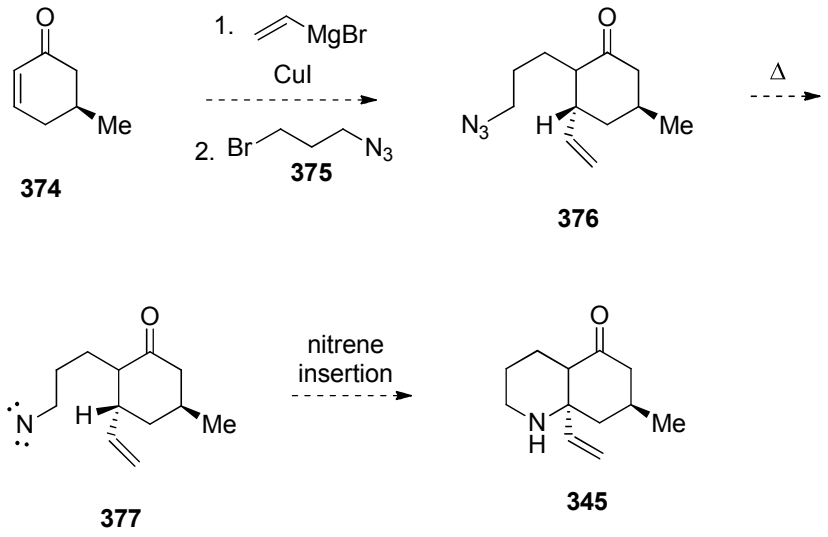
Alternatively, given the low yields in which **350** has been accessed, as well as the fact that the *N*-methyl substituent and the allyl side chain are not ideal for our approach, routes to **345** other than Wiesner's and Snider's should perhaps be considered. One possible approach would be an intramolecular Tsuji-Trost

allylation of (**372**) (Scheme 3.18). Formation of a π-allyl palladium species (**373**) would be followed by intramolecular nucleophilic attack to access vinyl fragment in **345**.



Scheme 3.18 Proposed synthesis of 345 *via* intramolecular Tsuji–Trost allylation.

Another possible way to access vinyl ketone **345** involves nitrene insertion to the C–H bond in (**377**) (Scheme 3.19). We envisage that **376** should be easily accessible from (**374**) by means of conjugate addition of a vinyl cuprate, followed by *α*-alkylation to derive (**376**). When heated, azide **376** should generate reactive nitrene species **377** and undergo C–H insertion to provide **345**.



Scheme 3.19 Proposed synthesis of 345 *via* nitrene insertion.

Chapter 4

Experimental

4. EXPERIMENTAL

4.1 General Methods

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen. In most cases, solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system.[142] All other solvents were purchased anhydrous from Fisher Scientifics or Sigma–Aldrich. TLC using aluminium backed plates precoated with Alugram®SIL G/UV 254 nm. Visualisation was accomplished by UV light, $KMnO_4$, DNPH, vanillin, ceric ammonium molybdate followed by gentle warming. Organic layers were routinely dried with anhydrous $MgSO_4$ and evaporated using a Büchi rotary evaporator. When necessary, further drying was facilitated by high vacuum. Flash column chromatography was carried out using Davisil LC 60 A silica gel (35-70 micron) purchased from Fisher Scientifics or high purity silica gel (60 Å, 200-400 mesh) and Celite® 545 from Sigma–Aldrich.

IR spectra were recorded on Perkin-Elmer 1600 FT IR spectrometer with only selected absorbances quoted as ν_{max} in cm^{-1}. NMR spectra were run in $CDCl_3$ or CD_3CN on either a Brüker Avance 250 (250 MHz), Brüker Avance 300 (300 MHz), Brüker Avance 400 (400 MHz) or Brüker Avance 500 (500 MHz) instrument and recorded at the following frequencies: proton (^1H – 250/500 MHz), carbon (^{13}C – 62.5/125 MHz). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; pent, pentet; hept, heptet; dd, doublet of doublets; m, multiplet and br, broad.

A micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Brüker Daltonik GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10µl of sample was injected into a 30:70 flow of water:acetonitrile at 0.6mL/min to the mass spectrometer. For each acquisition 10µL of calibrant of 5mM sodium formate was injected after the

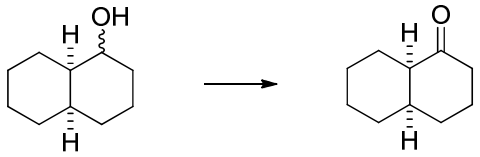
sample. The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula. Some samples for mass spectroscopy were sent to EPSRC NMSSC Swansea and analysed to obtain accurate mass using a Thermofisher LTQ Orbitrap XL ESI full-scan machine.

All capillary melting points were recorded using a Büchi 535 melting point apparatus. The readings were taken from a mercury-in-glass thermomether and were reported uncorrected as the meniscus point. All reactions were carried out at room temperature and under and under an atmosphere of N_2, unless otherwise stated.

Microwave assisted reactions were carried out in a Biotage Initiator 2.0 Eight (0-300W at 2.45 GHz).

4.2 Synthetic procedures for model system

cis-1-Decalone (138)[143]

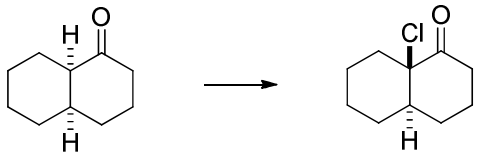


139 **138**

This was performed by adaptation of a literature procedure[144]. To a stirred solution of oxalyl chloride (3.06 mL, 35.6 mmol, 1.10 equiv) in DCM (20 mL) at –78 °C was added dimethyl sulfoxide (4.95 mL, 69.6 mmol, 2.15 equiv). The solution was stirred for 5 min and then decahydronaphthalen-1-ol **139** (5.00 g, 32.4 mmol, 1.00 equiv) in dry THF (20 mL) was added. The reaction mixture was stirred for 90 min at –78 °C under nitrogen, and then Et_3N (22.5 mL, 162 mmol, 5.00 equiv) was added. After 5 min the solution was warmed to rt during 20 min, then water (20 mL) was added and the reaction mixture was transferred

to a separating funnel. The mixture was extracted with DCM (2 × 100 mL). The combined organic extracts were washed with brine (2 × 100 mL) and dried over $MgSO_4$, then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (25% EtOAc in petroleum ether) to give the title product **138** (4.42 g, 90%) as a pale yellow oil: R_f 0.70 (25% EtOAc in petroleum ether). Analytical data were consistent with those previously reported:[145,146] δ_H (300 MHz, $CDCl_3$) 2.46-2.20 (3 H, m), 2.15-1.67 (6H, m), 1.67-1.15 (7H, m); δ_C (125 MHz, $CDCl_3$); 213.1 (>*C*=O), 50.6 (CH_2-*C*H-CO-), 40.4 (2°), 39.1 (2°), 29.1 (2°), 27.7 (2°), 25.1 (2°), 24.5 (2°), 23.5 (2°), 23.1 (2°).

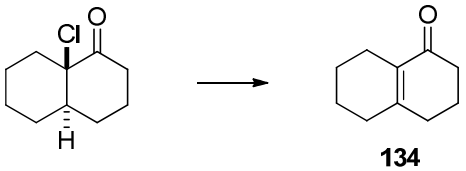
8a-Chloro-trans-1-decalone (140)[147]



138 **140**

This was performed by adaptation of a literature procedure.[148] To a stirred solution of **138** (4.42 g, 29.0 mmol, 1.00 equiv) in carbon tetrachloride (35 mL) at rt was added sulfuryl chloride (4.50 g, 33.4 mmol, 1.15 equiv) dropwise over a period of 20 min. The reaction mixture was stirred for 3 h, then transferred to a separating funnel and washed with water (2 × 50 mL), aq. sodium bicarbonate (2 × 50 mL) and aq. sodium chloride (2 × 50 mL). The organic phase was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. Purification by distillation under reduced pressure gave desired title ketone **140** (3.52 g, 70%) as a colourless oil; b.pt. 90–93°C (2.3 mbar). Analytical data were consistent with those previously reported:[147] δ_H (300 MHz, $CDCl_3$) 3.23-2.98 (2H, m), 2.64-2.57 (1H, m), 2.46-2.37 (4H, m), 2.36-1.21 (8H, m); δ_C (75 MHz, $CDCl_3$); 205.6 (>*C*=O), 76.6 (-CH_2-*C*Cl-), 47.3 (2°), 36.5 (2°), 36.3 (2°), 29.2 (3°), 27.6 (2°), 25.5 (2°), 24.4 (2°), 21.7 (2°).

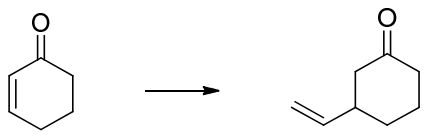
1,2,3,4,5,6,7,8-Octahydronaphthalen-1-one (134)[149]



140 **134**

This was performed by adaptation of a literature procedure.[148] To neat **140** (3.52 g, 20.5 mmol, 1.00 equiv) was added collidine (3.01 mL, 22.6 mmol, 1.10 equiv), then stirred and heated to 135 °C for 90 min. The reaction mixture was diluted with petroleum ether (25 mL) and filtered to separate solid collidine hydrochloride. The filtrate was washed with aq. hydrochloric acid (1.00 M, 2 × 25 mL), sat. aq. sodium bicarbonate (2 × 25 mL) and water (2 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by chromatography (5% EtOAc in petroleum ether) to give the title ketone **134** as a pale yellow oil (0.72 g, 23%): R_f 0.52 (25% EtOAc-petrol ether). Analytical data were consistent with those previously reported:[149,150] δ_H (250 MHz) 2.40-2.37 (2H, -C*H*$_2$-CO-), 2.23-2.17 (6H, m), 1.96-1.92 (2H, m), 1.61-1.59 (4H, m); δ_C (75 MHz, $CDCl_3$); 199.3 (>*C*=O), 157.0 (>*C*=C<), 132.2 (>C=*C*<), 37.8 (2°), 31.7 (2°), 31.4 (2°), 22.3 (2°), 22.1 (2°), 22.0 (2°), 21.9 (2°).

3-Vinylcyclohexanone (142)[151]

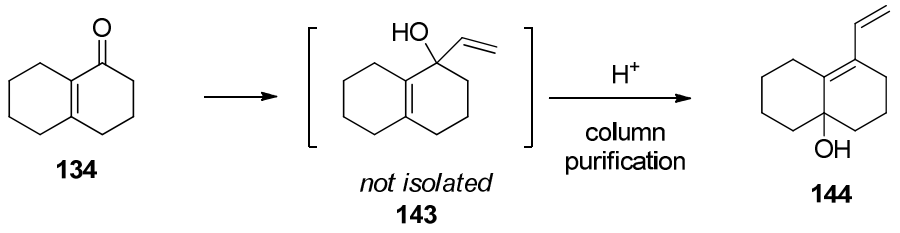


141 **142**

This was performed by adaptation of a literature procedure.[152] Copper (I) bromide-dimethyl sulphide complex (106 mg, 0.515 mmol, 10 mol%) was added

to a stirred solution of vinylmagnesium bromide (0.660 M, 15.6 mL, 10.4 mmol, 2.00 equiv) in THF at 0℃, then stirred for 15 min. A solution of cyclohex-2-enone **141** (500 mg, 5.20 mmol, 1.00 equiv) in dry THF (15 mL) was slowly added dropwise over 10 min. The resulting solution was stirred at 4–5℃ for 90 min. The reaction mixture then was added to a cold aq. solution of NH_4Cl (40 mL). The organic layer was separated and the aq. layer extracted with ether. The combined organic extracts were dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (5 to 10% EtOAc in petroleum ether) to give the title vinyl ketone **142** (323 mg, 50%) as a colourless oil; R_f 0.35 (10% EtOAc in petroleum ether). Analytical data were consistent with those previously reported[151,153]: δ_H (250 MHz, $CDCl_3$) 5.63-5.50 (1H, m, CH_2-C*H*-), 4.93-4.86 (2H, m, C*H*$_2$-CH-), 2.30-1.20 (11H, m); δ_C (75 MHz, $CDCl_3$); 200.2 (>*C*=O), 151.1 (CH_2-*C*H-), 130.3 (*C*H_2-CH-), 38.5 (2°), 26.0 (2°), 23.1 (2°).

1-Vinyl-,2,3,4,4a,5,6,7,8-octahydronaphthalen-4a-ol (144)



134 *not isolated* **143** **144**

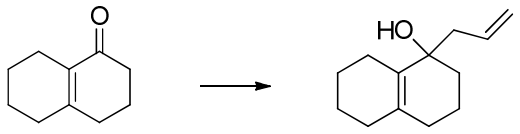
This was performed by adaptation of a literature procedure.[152] Copper (I) bromide-dimethyl sulfide complex (67.0 mg, 0.325 mmol, 0.500 equiv) was added to a stirred solution of vinylmagnesium bromide (1.40 M, 0.942 mL, 1.32 mmol, 2.00 equiv) in THF at 0℃, then stirred for 15 min. A solution of 3,4,5,6,7,8-hexahydronaphthalen-1(2H)-one **134** (100 mg, 0.665 mmol, 1.00 equiv) in dry THF (5 mL) was slowly added dropwise over 10 min period. The resulting solution was stirred at 0–5℃ for 2 h. The reaction mixture then was added to a cooled to 0 ºC aq. solution of NH_4Cl (3 × 10 mL). The organic layer

was separated and the aqueous layer extracted with Et_2O (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (5 to 50% EtOAc in petroleum ether) to give the title alcohol **144** (27.8 mg, 24%) as a colourless oil; R_f 0.66 (25% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 6.84 (1H, dd, *J* 17.0, 11.0 Hz, CH_2-C*H*-), 5.26 (1H, dd, J_{trans} 17.0, 1.0 Hz, CH_2-CH-), 5.07 (1H, d, J_{cis} 11.0 Hz, CH_2-CH-), 2.83-2.78 (1H, m, -O*H*), 2.49-0.70 (14 H, m); δ_C (75 MHz, $CDCl_3$) 138.9 (CH_2=*C*H-), 134.5 (CH_2=CH-*C*<), 129.3 (4°), 113.4 (*C*H_2=CH-), 70.0 (>*C*-OH), 40.9 (2°), 39.6 (2°), 27.3 (2°), 26.1 (2°), 25.0 (2°), 21.7 (2°), 18.4 (2°); ν_{max} (film), 3426, 2922, 2852, 1460, 1377, 1179, 907, 733 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{18}O - H_2O + H)^+$ 161.1325, found, 161.1322.

*1-vinyl-1,2,3,4,5,6,7,8-octahydronaphthalen-1-ol (**143**)*

δ_H (300 MHz, $CDCl_3$) 5.81 (1H, dd, *J* 17.0, 10.5 Hz, CH_2-C*H*-), 5.20 (1H, dd, J_{trans} 17.0, 1.5 Hz, CH_2-CH-), 5.10 (1H, dd, J_{cis} 10.5, 1.5 Hz, CH_2-CH-), 2.41-1.18 (15 H, m); δ_C (75 MHz, $CDCl_3$) 143.6 (CH_2=*C*H-), 133.0 (>*C*(-CH_2-)=C<), 128.7 (>C=*C*-($C^{4°}$)<), 112.7 (*C*H_2=CH-), 68.1 (>*C*-O*H*), 37.8 (2°), 30.7 (2°), 30.6 (2°), 24.0 (2°), 23.1 (2°), 22.8 (2°), 18.8 (2°); TOF-ESI+ *m/z* calculated for $(C_{12}H_{18}O - H_2O + H)^+$ 161.1325, found, 161.1327.

1-Allyl-1,2,3,4,5,6,7,8-octahydronaphthalen-1-ol (160)

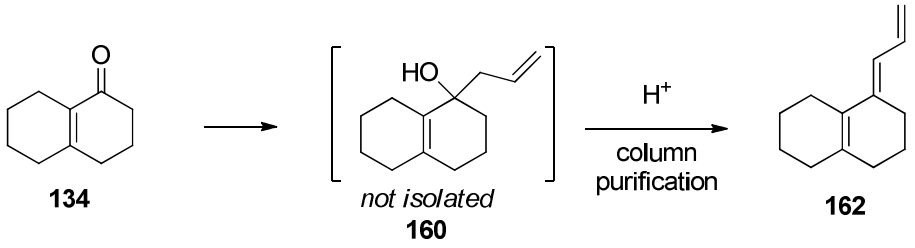


134 **160**

This was performed by adaptation of a literature procedure.[152] To a freshly prepared allylmagnesium bromide solution (0.640 M, 1.70 mL, 2.66 mmol, 2.00 equiv) ketone **134** (200 mg, 1.33 mmol, 1.00 equiv) in THF (10 mL) was added

and stirred at –78 ºC for 30 min. The reaction mixture then was quenched with NH_4Cl (2 × 20 mL) cooled to 0 ºC aq. and extracted with Et_2O (2 × 15 ml). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure then purified by column chromatography (2.5 to 20% EtOAc in petroleum ether and 1% Et_3N) to give the title alcohol **160** (104 mg, 41%) as colourless oil; R_f 0.59 (25% EtOAc in petrol ether); δ_H (500 MHz, $CDCl_3$) 5.72 (1H, ddt, *J* 16.5, 10.5, 7.0 Hz, allyl CH_2=C*H*-), 5.06 (1H, d, J_{trans} 16.5 Hz, allyl -CH=CH_2), 5.05 (1H, d, J_{cis} 10.0 Hz, allyl -CH=CH_2), 2.37-2.30 (2H, dd, *J* 7.0, 1.0 Hz, -CH_2-CH=CH_2), 2.21-2.17 (1H, m), 1.98-1.82 (5H, m), 1.74-1.56 (7H, m), 1.49-1.36 (2H, m); δ_C (125 MHz, $CDCl_3$) 134.5 (-*C*H=CH_2), 133.1 (>*C*=C<), 131.2 (>C=*C*<), 117.7 (-CH=*C*H_2), 71.6 (>C(O*H*)-), 43.5 (-*C*H_2-CH=CH_2), 35.9 (2°), 30.9 (2°), 30.8 (2°), 23.3 (2°), 23.2 (2°), 22.7 (2°), 18.6 (2°); ν_{max} (film) 3380, 2927, 2858, 2828, 1436, 1365, 1168, 1089, 974 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{13}H_{20}O + Na)^+$, 215.1411; found, 215.1404.

(E)-1-Allylidene-1,2,3,4,5,6,7,8-octahydronaphthalene (162)

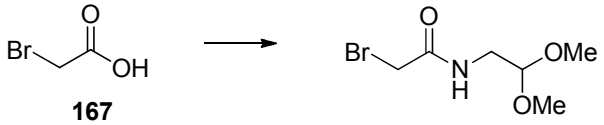


134 *not isolated* **160** **162**

To a freshly prepared allylmagnesium bromide solution (0.120 M, 4.87 mL, 0.585 mmol, 2.00 equiv) ketone **134** (44.0 mg, 0.292 mmol, 1.00 equiv) in THF (2 mL) was added and stirred at rt for 90 min. The reaction mixture was washed with cooled to 0 ºC aq. NH_4Cl solution (2 × 20 mL) and extracted with Et_2O (2 × 15 ml). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure then purified by column chromatography (eluents used: 2.5 to 10% EtOAc in petroleum ether and 1% Et_3N) to give the title compound **162** (23.0 mg, 45%); R_f 0.59 (25% EtOAc in petrol ether); δ_H

(300 MHz, $CDCl_3$) 6.72 (1H, ddd, *J* 16.5, 11.0, 10.0 Hz, CH_2=C*H*-), 6.02 (1H, d, *J* 11.0 Hz, >C=C*H*-), 5.17 (1H, dd, J_{trans} 16.5, 1.5 Hz, -CH=CH_2), 5.02 (1H, dd, J_{cis} 10.0, 1.5 Hz, -CH=CH_2), 2.46 (2H, t, *J* 6.0 Hz), 2.21-2.14 (2H, m), 2.09-2.01 (4H, m), 1.71-1.53 (6H, m); δ_C (75 MHz, $CDCl_3$) 138.9 (>*C*=C<), 137.8 (>*C*=CH-), 134.1 (>C=*C*<), 128.7 (-*C*H=CH_2), 120.5 (>C=*C*H-), 115.9 (-CH=*C*H_2), 32.4 (2°), 32.3 (2°), 30.1 (2°), 26.8 (2°), 25.4 (2°), 23.6 (2°), 22.9 (2°); ν_{max} (film) 2922, 2854, 1513, 1454, 1377, 1363, 1259, 1043, 984, 889 cm^{-1}. TOF-ESI+ *m/z* calculated for $(C_{13}H_{18} + H)^+$, 175.1481; found, 175.1477.

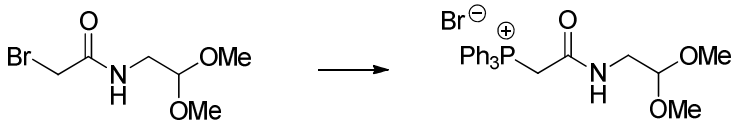
2-Bromo-N-(2,2-dimethoxyethyl)acetamide (165)



167 **165**

To a solution of bromoacetic acid **167** (2.77 g, 20.0 mmol, 1.00 equiv) and DMAP (122 mg, 1.00 mmol, 5 mol%) in DCM (100 mL), aminoacetaldehyde dimethyl acetal (2.11 g, 20.0 mmol, 1.00 equiv) was added dropwise followed by addition of N, N'-diisopropylcarbodiimide (3.09 mL, 2.52 g, 20.0 mmol, 1.00 equiv). The reaction mixture was stirred at rt for 14 h. Precipitated urea was filtered and washed with DCM (2 × 25 mL). The filtrate then was concentrated under reduced pressure and purified by column chromatography (40% EtOAc in petroleum ether) to give the title acetamide **165** (3.04 g, 67%) as a pale yellow oil; R_f 0.31 (50% EtOAc in petrol ether); δ_H (250 MHz, $CDCl_3$) 6.67 (1H, br, NH), 4.38 (1H, t, *J* 5.0 Hz, -C*H*-$(OCH_3)_2$), 3.86 (2H, s, -CH_2Br), 3.42 (2H, d, *J* 5.5 Hz -NH-CH_2-), 3.39 (6H, s, -OCH_3); δ_C (62.5 MHz, $CDCl_3$) 165.6 (>*C*=O), 102.2 (-*C*H$(OCH_3)_2$), 54.4 (-OCH_3), 41.5 (-NH-*C*H_2-), 28.9 (-*C*H_2Br); ν_{max} (film) 3292, 3084, 2941, 2835, 1654, 1539, 1430, 1387, 1366, 1193, 1125, 1072, 1053, 973, 932, 885, 819 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_6H_{12}BrNO_3 + Na)^+$, 247.9898; found, 247.9889.

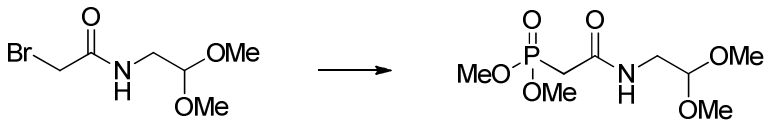
(2-(2,2-Dimethoxyethylamino)-2-oxoethyl)triphenylphosphonium bromide (166)



165 **166**

This was performed by adaptation of a literature procedure.[154] The acetamide **165** (800 mg, 5.53 mmol, 1.00 equiv) was dissolved in a 1:3 ratio mixture of THF and Et_2O (60 mL), and to this solution, triphenylphosphine (1.85 g, 7.07 mmol, 2.00 equiv) was added in one portion and left to stir at rt. After 45 min the clear reaction solution became turbid. After stirring for 15 h at rt, white precipitate of the phosphoniumsalt was collected by filtration and rinsed with Et_2O (50 mL) and hexanes (50 mL) to remove residual triphenylphosphine. The crude was dissolved in DCM (1 mL) and precipitated with hexane (10 mL), separated from solvents and dried under high vacuum to give the title salt **166** (1.15 g, 67%) as a white solid; m.pt. 143–145 °C; δ_H (300 MHz, $CDCl_3$) 9.34 (1H, t, *J* 5.5 Hz, -N*H*-CH_2-), 7.85-7.74 9H, m, Aryl C-*H*), 7.68-7.60 (6H, m, Aryl C-*H*), 5.07 (2H, d, *J* 14.0 Hz, Ph_3P^+-C*H*$_2$-CO-), 4.42 (1H, t, *J* 6.0 Hz, -NH-C*H*$(OCH_3)_2$), 3.27 (6H, s, -CH(OC*H*$_3)_2$), 3.23 (2H, d, *J* 5.5 Hz-NH-C*H*$_2$-CH$(OCH_3)_2$); δ_C (75 MHz, $CDCl_3$) 162.6 (1C, d, $^1J_{CP}$ 5.0 Hz, Ph_3P^+-CH_2-*C*O-NH-), 134.9 (1C, d, $^1J_{CP}$ 3.0 Hz, *Ph*$_3P^+$-CH_2-*C*O-), 133.9 (1C, d, $^1J_{CP}$ 10.5 Hz, *Ph*$_3P^+$-CH_2-*C*O-), 130.0 (1C, d, $^1J_{CP}$ 12.5 Hz, *Ph*$_3P^+$-CH_2-*C*O-), 118.3 (1C, d, $^1J_{CP}$ 87.5 Hz, *Ph*$_3P^+$-CH_2-*C*O-), 101.0 (-CH_2-*C*H$(OCH_3)_2$), 53.2 (-CH(O*C*H$_3)_2$), 41.1 (-*C*H$_2$-*C*H$(OCH_3)_2$), 32.3 (1C, d, $^1J_{CP}$ 59.0 Hz,Ph_3P^+-*C*H$_2$-CO-); ν_{max} (film), 3054, 2899, 1668, 1550, 1458, 1336, 1110, 916, 719 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{24}H_{27}NO_3P)^+$, 408.1723, found, 408.1718.

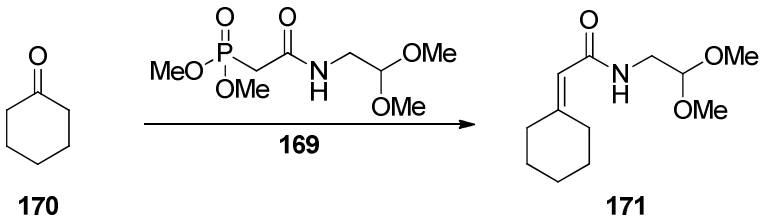
Dimethyl 2-(2,2-dimethoxyethylamino)-2-oxoethylphosphonate (169)



165 **169**

This was performed by adaptation of a literature procedure.[62] A mixture of 2-bromo-*N*-(2,2-dimethoxyethyl)acetamide **165** (1.59 g, 7.03 mmol, 1.00 equiv) and trimethyl phoshpite (2.48 mL, 21.1 mmol, 3.00 equiv) was heated neat for 16 h at 105–110 °C. The reaction mixture was cooled, volatile materials were removed by vacuum distillation, after which the crude product was purified by column chromatography (5% MeOH in DCM) to give the title phosphonate **169** (774 mg, 43%) as a colourless oil; R_f 0.11 (5% MeOH in DCM); δ_H (300 MHz, $CDCl_3$) 6.82 (1H, br, -CO-N*H*-), 4.35 (1H, t, *J* 5.5 Hz, -CH_2-C*H*$(OCH_3)_2$), 3.74 (6H, d, $^3J_{PH}$ 11.0 Hz, -CH_2-PO(OC*H*$_3)_2$), 3.36 (2H, d, *J* 5.5 Hz, -NH-C*H*$_2$-CH$(OCH_3)_2$), 3.33 (6H, s, -NH-CH_2-CH(OC*H*$_3)_2$), 2.84 (2H, d, $^2J_{PH}$ 21.0 Hz, -CO-C*H*$_2$-PO$(OCH_3)_2$); δ_C (75 MHz, $CDCl_3$) 163.9 (1C, d, $^2J_{CP}$ 18 Hz, $(OCH_3)_2$P-CH_2-*C*O-), 102.5 (-*C*H$(OCH_3)_2$), 54.0 (-CH(O*C*H$_3)_2$), 53.0 (2C, d, $^2J_{CP}$ 27 Hz, (O*C*H$_3)_2$P-CH_2-CO-), 41.1 (-NH-*C*H$_2$-CH$(OCH_3)_2$), 34.1 (1C, d, $^1J_{CP}$ 131.0 Hz, $(OCH_3)_2$P-*C*H$_2$-CO-); ν_{max} (film), 3447, 3289, 3084, 2997, 2955, 1655, 1552, 1449, 1241, 1207, 1127, 1026, 926, 873 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_8H_{18}NO_6P + H)^+$, 256.0949, found, 256.0926; calculated for $(C_8H_{18}NO_6P + Na)^+$, 278.0769, found, 278.0749.

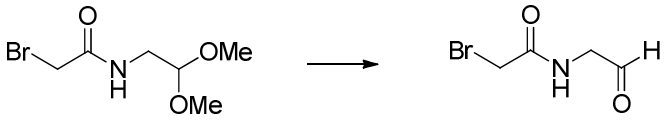
2-Cyclohexylidene-N-(2,2-dimethoxyethyl)acetamide (171)



170 **171**

This was performed by adaptation of a literature procedure.[62] A stirred solution of phosphonoacetamide **169** (0.936 g, 0.366 mmol, 1.00 equiv) in dry THF (15 mL) was treated with DBU (0.135 mL, 1.09 mmol, 3.00 equiv) and lithium chloride (46.2 mg, 1.09 mmol, 3.00 equiv) at rt. After stirring for 10 min, **170** (0.037 mL, 0.366 mmol, 1.00 equiv) was added and the reaction mixture was stirred for 1.5 h at rt. The reaction mixture was then quenched by addition of a sat. NH_4Cl solution (3 × 10 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) followed by brine (20 mL), then were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (50% EtOAc in petroleum ether) to give the title amide **171** (22.2 mg, 27%) as colourless oil; R_f 0.60 (50% EtOAc in petrol ether); δ_H (300 MHz, $CDCl_3$) 5.58 (1H, br, -CO-N*H*-CH_2-), 5.49 (1H, s, >C=C*H*-CONH-), 4.38 (1H, t, *J* 5.0 Hz, -CH_2-C*H*$(OCH_3)_2$), 3.42 (2H, d, *J* 5.5 Hz, -CO-NH-C*H*$_2$-CH$(OCH_3)_2$), 3.38 (6H, s, -CH_2-CH(OC*H*$_3)_2$), 2.82-2.77 (2H, m, -C*H*$_2$-C(4º)-CH_2-), 2.15-2.11 (2H, m, -CH_2-C(4º)-C*H*$_2$-), 1.64-1.54 (6H, m, -CH_2-C*H*$_2$-C*H*$_2$-C*H*$_2$-CH_2-); δ_C (75 MHz, $CDCl_3$) 167.1 (=CH-*C*O-NH-), 158.2 (>*C*=CH-CO-NH-), 115.3 (>C=*C*H-CONH-), 102.8 (-CH_2-*C*H$(OCH_3)_2$), 54.4 (-CH_2-CH(O*C*H$_3)_2$), 40.5 (-CO-NH-*C*H$_2$-), 37.7 (2°), 29.6 (2°), 28.5 (2°), 27.7 (2°), 26.3 (2°); ν_{max} (film), 3302, 2993, 2928, 2854, 2834, 1658, 1632, 1535, 1447, 1246, 1226, 1187, 1128, 1056, 973, 851, 781, 652 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{21}NO_3 + H)^+$, 228.1599, found, 228.1582; calculated for $(C_{12}H_{21}NO_3 + Na)^+$, 250.1419, found, 250.1401.

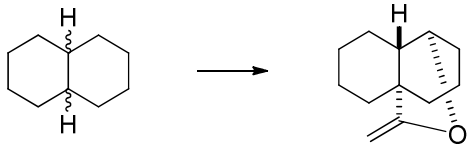
2-Bromo-N-(2-oxoethyl)acetamide (173)



165 **173**

To a solution of acetamide **165** (0.057 g, 0.252 mmol, 1.00 equiv) in DCM (5 mL) TFA (0.500 mL, 6.52 mmol, 25.8 equiv) was added dropwise and stirred under N_2 at rt for 1 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (25 to 75% EtOAc in petroleum ether) to give the title compound **173** (0.006 g, 13%) as a colourless oil; R_f 0.13 (50% EtOAc in petrol ether); δ_H (500 MHz, $CDCl_3$) 9.65 (1H, s, >NH-CH_2-C*H*O), 7.23 (1H, br s, >N*H*-CH_2-CHO), 4.22 (2H, d, *J* 5.0 Hz, >NH-C*H*$_2$-CHO), 3.91 (2H, s, -NH-CO-C*H*$_2$Br); δ_C (125 MHz, $CDCl_3$) 195.4 (>NH-CH_2-*C*HO), 166.0 (-NH-*C*O-CH_2Br), 50.5 (>NH-*C*H_2-CHO), 28.3 (-NH-CO-*C*H_2Br); ν_{max} (film) 3330, 2963, 1636, 1541, 1443, 1417, 1384, 1278, 1224, 1121, 1014, 923, 885, 864, 715, 694 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_4H_6NO_2Br + H)^+$, 179.9660; found, 179.9679.

(1R*,4aS*,8aS*)-9-Methylenedecahydro-1,4a-(epoxymethano)naphthalene (176)

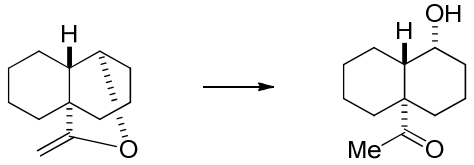


175 **176**

This was performed in accordance with a literature procedure.[67] Acetyl chloride (89.4 mL, 1.25 mol, 2.40 equiv) was gradually added with stirring over 15 min. to a cooled (<25 °C) mixture of aluminium chloride (104 g, 0.786 mol, 1.50 equiv) in DCM (225 mL). The resulting yellow-brown solution was decanted into

a flask, cooled to <10 °C, and decalin **175** (80.9 mL, 0.524 mol, 1.00 equiv) was gradually added over 30 min with stirring and cooling to keep the temperature of the reaction mixture below 10 °C. After a further 2 h at 10–15 °C, the mixture was gradually added to vigorously stirred slurry of crushed ice (1 kg) and water. The lower organic layer was separated and, together with DCM extracts of the aqueous layer, washed several times with ice-cold water and dried over $MgSO_4$, then filtered. The filtrate was concentrated under reduced pressure. Fractional distillation of the residual brown oil gave crude product (b.p. 82–85 °C at 5.8 Torr) which was then further purified by refluxing with $LiAlH_4$ (0.5 g) in dry Et_2O (30 mL) for 30 min. Excess of hydride was destroyed by cautious addition of EtOAc (5 mL), and ice-cold dilute sulfuric acid (50 mL, 0.5 N) was gradually added to the cooled mixture. The ethereal layer was separated and, with further ethereal extracts of aqueous layer, was washed with water (2 × 50 mL) and dried over $MgSO_4$, then filtered. The filtrate was concentrated under reduced pressure. Further distillation afforded the pure title enol ether **176** (22.8 g, 25%) as a pale yellow oil; b.pt. 65 °C at 1.5 Torr; δ_H (250 MHz, $CDCl_3$) 4.22 (1H, dt, *J* 1.0, 0.5 Hz, >C*H*-O-), 4.03 (1H, d, *J* 4.5 Hz, =CH_2), 3.66 (1H, d, *J* 1.5 Hz, =CH_2), 0.86-1.07 (15H, m); δ_C (75 MHz, $CDCl_3$) 166.0 (>*C*=CH_2), 80.5 (>*C*H-O-), 76.9 (=*C*H_2), 50.0 (3°), 46.2 (4°), 39.5 (2°), 31.3 (2°), 30.2 (2°), 26.5 (2°), 24.9 (2°), 22.1 (2°), 18.9 (2°); ν_{max} (film) 2927, 2860, 1679, 1455, 1369, 1198, 1106, cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{18}O + H)^+$, 179.1435, found, 179.1422.

1-((1R*,4aS*,8aS*)-1-Hydroxydecahydronaphthalen-4a-yl)ethanone (177)

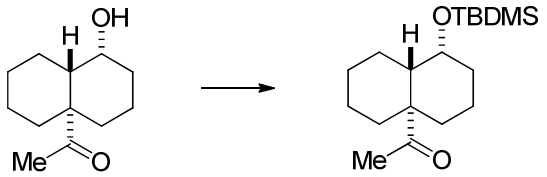


176 **177**

This was performed in accordance with a literature procedure.[68] A mixture of vinyl ether **176** (20.1 g, 113 mmol, 1.00 equiv) in Et_2O (150 mL) and dilute

sulfuric acid (1.00 N, 290 mL) was stirred and refluxed for 2.5 h. The ether layer was separated and, aqueous layed was washed with ether (2 × 100 mL) and combined organic extracts was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was washed with cold light petroleum to give the title product **177** (11.2 g, 51%), which crystallised from light petrol; m.pt. 60–61 °C; R_f 0.54 (50% EtOAc in petroleum ether). Crystals of **177** suitable for X-ray diffraction were grown by slow diffusion of petrol ether vapour into a solution of **177** in MeOH; δ_H (300 MHz, $CDCl_3$) 5.46 (1H, dd, *J* 8.5, 0.5 Hz, -O*H*), 3.70 (1H, dq, *J* 8.5, 3.0 Hz, >C*H*-OH), 2.17 (1H, s, -CO-CH_3), 1.96-1.64 (6H, m), 1.53-1.16 (8H, m), 1.21-0.99 (1H, m); δ_C (75 MHz, $CDCl_3$) 217.5 (>*C*O-CH_3), 68.9 (>*C*H-OH), 56.1 (3°), 48.8 (4°), 39.5 (2°), 36.9 (2°), 35.0 (2°), 26.9 (>CO-*C*H_3), 26.4 (2°), 25.7 (2°), 24.2 (2°), 17.2 (2°); ν_{max} (film), 3751, 3649, 3351, 2927, 2860, 2554, 2350, 2159, 2032, 1977, 1679, 1455, 1369, 1253, 1198, 1177, 1137, 1106, 1066, 1041, 1009, 981, 947, 915, 884, 778, 720, 644, 618 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{20}O_2 + H)^+$, 197.1541, found, 197.1514; calculated for $(C_{12}H_{20}O_2 + Na)^+$, 219.1361, found, 219.1327.

1-((1R,4aS*,8aS*)-1-((tert-Butyldimethylsilyl)oxy)decahydronaphthalen-4a-yl)ethanone (191)*



177 **191**

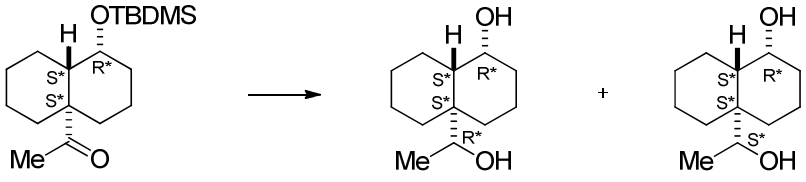
tert-Butyldimethylsilyl chloride (0.370 g, 2.46 mmol, 1.25 equiv) was slowly added to a solution of hydroxyketone **177** (0.387 g, 1.97 mmol, 1.00 equiv) and imidazole (0.537 g, 7.89 mmol, 4.00 equiv) in dry DMF (6 mL) with stirring at 0 °C. The reaction mixture was allowed to warm to rt, stirred for 17 h, and poured into an ice cold aq. solution of LiCl (20 mL). The aqueous mixture was extracted

with EtOAc (3 × 15 mL), and then the organic layer was washed with brine (3 × 10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to furnish the crude product which was purified by column chromatography (1% to 5% EtOAc in petroleum ether) to give the title ketone **191** (0.58 g, 95%) as a colourless oil; R_f 0.53 (5% EtOAc in pertroleum ether); δ_H (300 MHz, $CDCl_3$) 3.74 (1H, br s, >C*H*-OSi$(CH_3)_2$-), 2.16 (3H, s, -CO-C*H*$_3$), 1.86-1.68 (14H, m), 1.57-1.02 (11H, m), 0.85 (9H, s, -Si$(CH_3)_2$-C(C*H*$_3)_3$), 0.01 (3H, s, -Si(C*H*$_3)_2$-C$(CH_3)_3$), -0.02 (3H, s, -Si(C*H*$_3)_2$-C$(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 210.5 (>*C*O-CH_3), 71.8 (>*C*H-OSi$(CH_3)_2$-), 52.2 (3°), 48.7 (4°), 38.9 (2°), 38.1 (2°), 35.1 (2°), 28.2 (>Si$(CH_3)_2$-*C*$(CH_3)_3$), 27.1 (2°), 26.5 (>CO-*C*H_3), 25.7 (>Si$(CH_3)_2$-C(*C*$H_3)_3$), 21.3 (2°), 18.8 (2°), 18.0 (2°), -4.8 (>Si(*C*$H_3)_2$-C$(CH_3)_3$), -4.8 (>Si(*C*$H_3)_2$-C$(CH_3)_3$); ν_{max} (film), 2929, 2855, 1702, 1461, 1445, 1361, 1344, 1251, 1202, 1158, 1069, 1049, 1017, 983, 954, 925, 900, 866, 837, 807, 774, 650 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{18}H_{34}O_2Si + H)^+$, 311.2406, found, 311.2406; calculated for $(C_{18}H_{34}O_2Si + Na)^+$, 333.2225, found, 333.2236.

(1R*,4aS*,8aS*)-4a-((R*)-1-Hydroxyethyl)decahydronaphthalen-1-ol (193)

(1R*,4aS*,8aS*)-4a-((S*)-1-Hydroxyethyl)decahydronaphthalen-1-ol (194)

Procedure A



191 **193** **194**

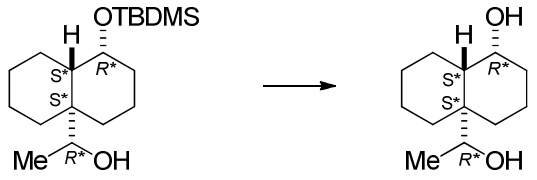
A solution of silyl ether **191** (550 mg, 1.77 mmol, 1.00 equiv) in dry ether (10 mL) was added to a suspension of $LiAlH_4$ (100 mg, 2.65 mmol, 1.50 equiv) in

dry ether (10 mL). The mixture was stirred at rt for 17 h. Water was added until effervescence ceased, followed by aq. HCl (1.0 M) until all unreacted $LiAlH_4$ was consumed. After extraction with ether (3 × 15 mL), the combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was purified by column chromatography (25% to 50% EtOAc in petroleum ether) to give two diastereomers **193** and **194**:

Diol **193** (270 mg, 77%) white solid; m.pt. 120–121 °C. Crystals of **193** suitable for X-ray diffraction were grown by slow diffusion of petrol ether vapour into a solution of **193** in chloroform. R_f 0.14 (25% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 5.64 (2H, s, -O*H*), 4.28 (1H, q, *J* 6.0 Hz, -C*H*(CH_3)OH), 3.69-3.66 (1H, m, >C*H*-OH), 2.16-1.76 (5H, m), 1.56-1.28 (8H, m), 1.14 (3H, d, *J* 6.0 Hz, -C(OH)-C*H*$_3$), 0.94-0.72 (2H, m); δ_C (75 MHz, $CDCl_3$) 69.9 (-*C*H(CH_3)-OH), 66.3 (>*C*H-OH), 50.4 (HO-CH(CH_3)-C(4°)-*C*H<), 41.5 (HO-CH(CH_3)-*C*(4°)-CH<), 39.5 (2°), 34.4 (2°), 33.9 (2°), 27.1 (2°), 25.2 (2°), 21.8 (2°), 18.9 (2°), 17.1 (-C(OH)-*C*H$_3$); ν_{max} (film), 3152, 2921, 2867, 1456, 16374, 1319, 1261, 1196, 1155, 1123, 1088, 1051, 1013, 987, 956, 934, 903, 885, 866, 843, 798, 774, 731, 667 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{22}O_2 + H)^+$, 199.1698, found, 199.1684; calculated for $(C_{12}H_{22}O_2 + Na)^+$, 221.1517, found, 221.1507.

Diol **194** (22 mg, 6%) as a white solid; R_f 0.37 (25% EtOAc in pertroleum ether); δ_H (250 MHz, $CDCl_3$) 4.45 (1H, q, *J* 6.5 Hz, -C*H*(CH_3)OH), 3.92-3.88 (1H, m, (>C*H*-OH), 2.72 (2H, s, -OH), 2.36-2.17 (1H, m, HO-CH(CH_3)-C(4°)-C*H*<), 1.98-1.24 (12H, m), 1.17 (3H, d, *J* 6.5 Hz, -CH(C*H*$_3$)OH), 0.97-0.70 (2H, m); δ_C (75 MHz, $CDCl_3$) 72.2 (-*C*H(CH_3)OH), 71.8 (>*C*H-OH), 50.7 (HO-CH(CH_3)-C(4°)-*C*H<), 39.1 (HO-CH(CH_3)-*C*(4°)-CH<), 38.3 (2°), 37.6 (2°), 34.6 (2°), 28.5 (2°), 27.4 (2°), 22.9 (2°), 18.4 (2°), 17.2 (CH_3); ν_{max} (film), 3298, 2924, 2850, 1452, 1370, 1335, 1307, 1261, 1195, 1152, 1126, 1092, 1068, 1042, 1030, 1008, 9889, 976, 953, 928, 903, 881, 845, 803, 779, 731, 674, 631 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{22}O_2 + H)^+$, 199.1698, found, 199.1683; calculated for $(C_{12}H_{22}O_2 + Na)^+$, 221.1517, found, 221.1499.

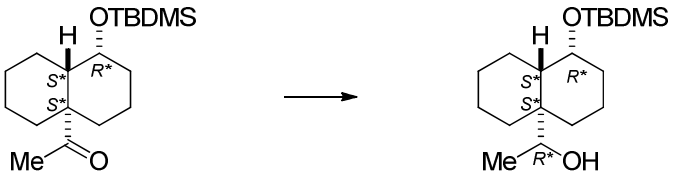
Procedure B



192 **193**

To a solution of silyl ether **192** (288 mg, 0.921 mmol, 1.00 equiv) in dry THF (5 mL) TBAF solution in THF (1.00 M, 1.01 mL, 1.01 mmol, 1.10 equiv) was added at º0 C. The mixture was stirred at rt for 16 h before being diluted it with DCM (20 mL), washed with water (2 × 15 mL), brine (20 mL), the combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was purified by column chromatography (25% to 50% EtOAc in petroleum ether) to give the title diol **193** (0.147 g, 81%) as a white solid. Spectroscopic data correspond to those reported in procedure A.

(R*)-1-((1R*,4aS*,8aS*)-1-((tert-Butyldimethylsilyl)oxy)decahydronaphthalen-4a-yl)ethanol (192)

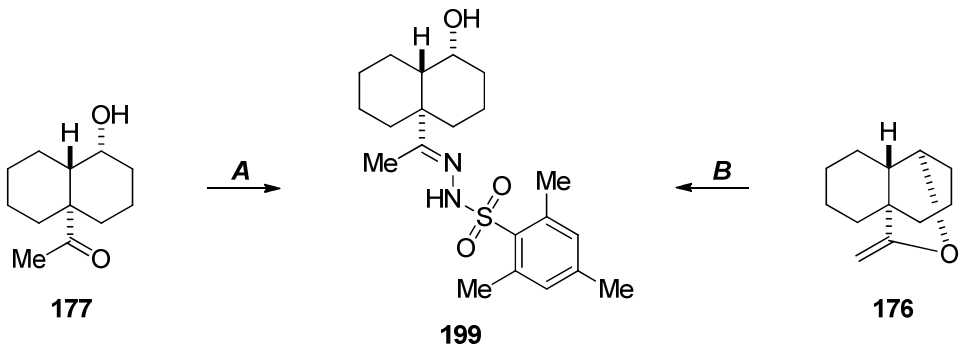


191 **192**

To a solution of ketone **191** (1.65 g, 5.31 mmol, 1.00 equiv) in dry DCM (20 mL) at –78 ℃ was added DIBAL-H (1.00 M in DCM; 7.97 mL, 7.97 mmol, 1.50 equiv). The reaction mixture was stirred at –78 ℃ for 5 min, then at rt for 1.5 h. The reaction mixture was diluted with EtOAc (150 mL) and poured into sat. aq. sodium potassium tartrate (150 mL) and water (150 mL). The reaction mixture was stirred vigorously for 30 min. The aqueous phase was washed with EtOAc

(2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by chromatography (25% EtOAc-petroleum ether) to give the title product **192** (1.15 g, 70%) as an colourless oil; R_f 0.88 (25% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 5.38 (1H, app s, OH), 4.26 (1H, q, *J* 6.0 Hz, -C*H*(CH_3)-OH), 3.81 (1H, q, *J* 3.0 Hz >C*H*-OH), 2.29-2.13 (1H, m), 2.08-1.94 (1H, m), 1.86-1.70 (3H, m), 1.59-1.21 (8H, m), 1.12 (3H, dd, *J* 6.0, 1.0 Hz, -CH(C*H*$_3$)-OH), 0.89 (9H, s, >Si(CH_3)$_2$-C(C*H*$_3$)$_3$), 0.86-0.68 (2H, m), 0.08 (6H, s, >Si(C*H*$_3$)$_2$-C(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 72.6 (>*C*H-O- Si(CH_3)$_2$-C(CH_3)$_3$), 65.7 (-*C*H(CH_3)-OH), 50.7 (HO-CHCH$_3$-C(4°)-*C*H<), 41.8 (2°), 39.6 (HO-CHCH$_3$-*C*(4°)-CH<), 34.1 (2°), 33.8 (2°), 27.1 (>Si(CH_3)$_2$-*C*(CH_3)$_3$), 25.88 (2°), 25.82 (>Si(CH_3)$_2$-C(*C*H$_3$)$_3$), 21.3 (2°), 19.0 (2°), 18.5 (2°), 16.4 (CH_3), -4.76 (>Si(*C*H$_3$)$_2$-C(CH_3)$_3$), -4.92 (>Si(*C*H$_3$)$_2$-C(CH_3)$_3$); ν_{max} (film), 3402, 2928, 2857, 1462, 1385, 1364, 1199, 1163, 1094, 1071, 981, 939, 822 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{18}H_{36}O_2Si + H)^+$, 313.2562, found, 313.2547; calculated for $(C_{18}H_{36}O_2Si + Na)^+$, 335.2382, found, 335.2374.

1-((1R*,4aS*,8aS*)-1-Hydroxydecahydronaphthalen-4a-yl)ethanone N-(2,4,6-trimethylbenzenesulfonyl)hydrazone (199)



177 **199** **176**

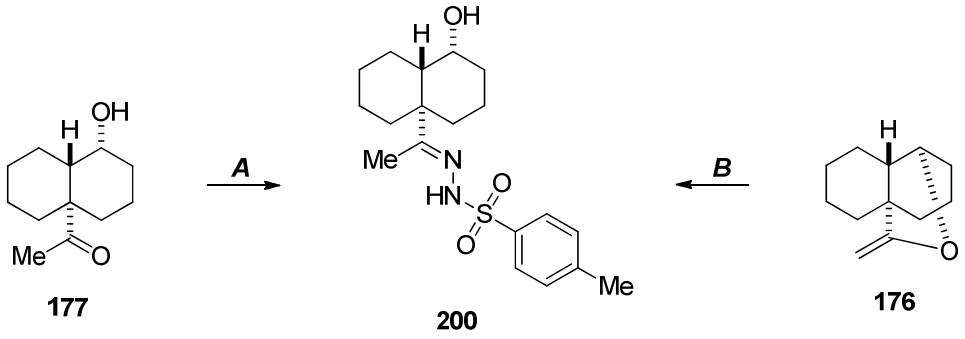
Procedure A

To a solution of hydroxyketone **177** (5.00 g, 25.4 mmol, 1.00 equiv) in ethanol (125 mL) was added 2,4,6-trimethylbenzenesulfonohydrazide (5.46 g, 25.4 mmol, 1.00 equiv), *p*-TSA (5 mol%) and 4Å molecular sieves. The reaction mixture was refluxed for 3 h. The reaction mixture was left to cool over 16 h, during which time the product crystallised. The precipitate was then filtered and washed with cold ethanol (2 × 50 mL), to give the desired hydrazone **199** (8.58 g, 86%) as a single isomer and a white solid; m.pt. 173–175 °C; R_f 0.47 (40% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 6.97 (2H, s, Ar-*H*), 5.33 (1H, br s, -N*H*-), 3.60 (1H, s br, -O*H*), 2.69 (6H, s, Ar-*o*-CH_3), 2.29 (3H, s, Ar-*p*-CH_3), 1.79 (3H, s, -CH_3), 1.82-1.76 (3H, m), 1.43-0.99 (12H, m) 0.65-0.52 (1H, m); δ_C (75 MHz, $CDCl_3$) 161.2 (CH_3-*C*=N-), 143.0 (Ar-*C*), 139.8 (Ar-*C*), 132.4 (Ar-*C*), 131.9 (Ar-*C*), 69.4 (>*C*-OH), 49.6 (3°), 49.0 (4°), 39.4 (2°), 37.5 (2°), 35.4 (2°), 27.3 (2°), 25.2 (2°), 23.0 (2°), 22.6 (-C(*C*H_3)=N-), 20.9 (2°), 17.2 (1°), 12.6 (1°); ν_{max} (film) 3360, 3261, 2938, 2857, 1636, 1604, 1446, 1380, 1338, 1161, 1110, 950, 891 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{21}H_{32}N_2O_3S + H)^+$, 393.2211, found, 393.2205; calculated for $(C_{21}H_{32}N_2O_3S + Na)^+$, 415.2031, found, 415.2018.

Procedure B

To a solution of enol ether **176** (6.93 g, 38.9 mmol, 1.00 equiv) in ethanol (125 mL) was added 2,4,6-trimethylbenzenesulfonohydrazide (8.33 g, 38.9 mmol, 1.00 equiv) and *p*-TSA (10 mol%). The reaction mixture was refluxed for 4 h. The reaction mixture was left to cool over 16 h, during which time the product crystallised. The precipitate was then filtered and washed with cold ethanol (3 × 30 mL), to give the desired hydrazone **199** (10.0 g, 66%) as a white solid. Spectroscopic data correspond to those reported in procedure A.

1-((1R*,4aS*,8aS*)-1-Hydroxydecahydronaphthalen-4a-yl)ethanone N-(4-trimethylbenzenesulfonyl)hydrazone (200)



Procedure A

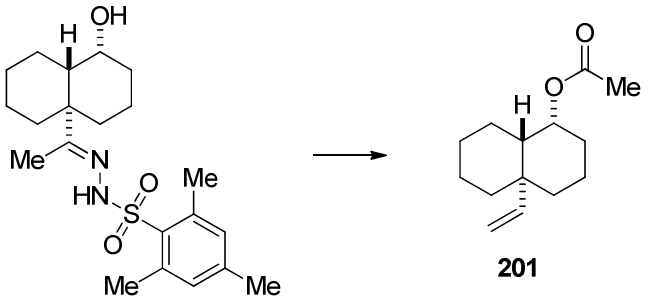
To a solution of hydroxyketone **177** (550 mg, 2.80 mmol, 1.00 equiv) in ethanol (15 mL) was added *p*-toluenesulfonyl hydrazide (520 mg, 2.80 mmol, 1.00 equiv), *p*-TSA (5.3 mg, 10 mol%) and 4Å molecular sieves. The reaction mixture was refluxed for 3 h. The reaction mixture was left to cool overnight, during which time the product crystallised. The precipitate was then filtered and washed with cold ethanol (2 × 10 mL), to give the desired hydrazone **200** (820 mg, 80%) as a single isomer and a white solid; m.pt. 174–176 °C; R_f 0.36 (30% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 8.26 (1H, br s, -N*H*-) 7.93 (2H, d, *J* 8.0 Hz, Ar-H), 7.32 (2H, d, *J* 8.0 Hz, Ar-H), 5.70 (1H, br s, -OH), 3.66-3.64

(1H, m, >C*H*-CH(OH)-), 2.41 (3H, s, Ar-CH_3), 1.84-1.70 (3H, m), 1.75 (3H, s, -C(CH_3)=N-), 1.49-1.00 (11H, m) 0.68-0.55 (1H, m); δ_C (75 MHz, $CDCl_3$) 162.5 (-*C*(CH_3)=N-), 144.2 (Ar-*C*), 135.4 (Ar-*C*), 129.7 (Ar-*C*), 128.1 (Ar-*C*), 69.3 (>C-OH), 49.6 (>*C*H-CH(OH)-), 49.1 (4°), 39.7 (2°), 37.2 (2°), 35.4 (2°), 27.1 (2°), 25.5 (2°), 23.0 (2°), 21.5 (-C(*C*H_3)=N-), 17.0 (2°), 13.2 (1°); ν_{max} (film) 3658, 3270, 2981, 2919, 2855, 1599, 1456, 1342, 1241, 1167, 1094, 994, 951, 812 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{19}H_{28}N_2O_3S + Na)^+$, 387,1777, found, 387,1777.

Procedure B

To a solution of enol ether **176** (13.9 g, 77.8 mmol, 1.00 equiv) in ethanol (175 mL) was added *p*-toluenesulfonyl hydrazide (14.5 g, 77.8 mmol, 1.00 equiv) and *p*-TSA (147 mg, 10 mol%). The reaction mixture was refluxed for 3 h. The reaction mixture was left to cool to rt. The precipitated product was then filtered and washed with cold ethanol (3 × 50 mL), to give the desired hydrazone **200** (15.7 g, 55%) as a white solid. Spectroscopic data correspond to those reported in procedure A.

(1R*,4aR*,8aS*)-4a-Vinyldecahydronaphthalen-1-yl acetate (201)

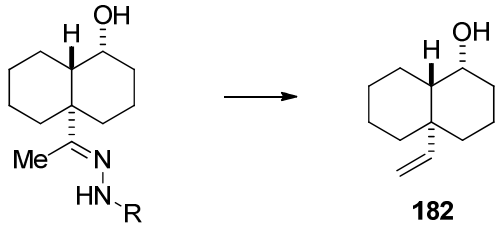


199 **201**

This was performed by adaptation of a literature procedure.[155] To a solution of hydrazide **199** (206 mg, 0.525 mmol, 1.00 equiv) in THF (10 mL), *n*-BuLi (0.740 M, 2.12 mL, 1.62 mmol, 3.05 equiv), was added dropwise within 5 min at –78

°C. Bright yellow reaction mixture was warmed up to rt and stirred for 1.5 h. The reaction mixture then was diluted with EtOAc (20 mL), washed with aqueous NH_4Cl solution (3 × 10 mL), brine (2 × 15 mL), water (15mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (2.5 to 10% EtOAc in petroleum ether) gave the title acetate **201** (76.6 mg, 66%) as a colourless oil; R_f 0.77 (25% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 6.51 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*=CH_2), 5.09 (1H, dd, J_{cis} 11.0, 1.5 Hz, -CH=CH_2), 4.99 (1H, dd, J_{trans} 17.5, 1.5 Hz, -CH=CH_2), 4.93 (1H, q, *J* 2.5 Hz, >C*H*($OCOCH_3$)-), 2.03 (3H, s, -OCH_3), 1.89-1.62 (6H, m), 1.58-1.10 (8H, m), 0.90-0.82 (1H, m); δ_C (75 MHz, $CDCl_3$) 170.7 (-O*C*OCH_3), 143.4 (-*C*H=CH_2), 111.7 (-CH=*C*H_2), 73.7 (>*C*H($OCOCH_3$)-), 48.1 (>*C*H-CH(OH)-), 42.4 (4°), 40.3 (2°), 40.2 (2°), 31.1 (2°), 26.9 (2°), 25.9 (2°), 21.9 (2°), 21.2 (2°), 17.4 (1°); ν_{max} (film) 2929, 2929, 2853, 1735, 1633, 1451, 1377, 1243, 1229, 1152, 1021, 907 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{14}H_{22}O_2 + Na)^+$, 245.1517, found, 245.1508.

(1R*,4aR*,8aS*)-4a-Vinyldecahydronaphthalen-1-ol (182)



R = *p*-Tol, **200**
Mes, **199**

182

Procedure A

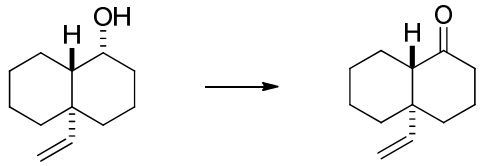
This was performed by adaptation of a literature procedure.[155] To a solution of mesityl hydrazone **199** (2.42 g, 6.17 mmol, 1.00 equiv) in Et_2O (40 mL) was added *n*-BuLi in hexanes (1.74 M, 10.8 mL, 18.8 mmol, 3.09 equiv), dropwise

over 10 min at –78 °C. Then bright yellow reaction mixture was warmed up to rt and the resulting orange solution then stirred for 1.5 h. The reaction mixture then was washed with aq. NH_4Cl solution (3 × 20 mL), brine (2 × 20mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (10 to 20% EtOAc in petroleum ether) gave the title product **182** (1.10 g, 99%) as a colourless oil; R_f 0.50 (25% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 6.55 (1H, dd, *J* 18.0, 11.0 Hz, -C*H*=CH_2), 5.07 (1H, dd, J_{cis} 11.0, 1.5 Hz, -CH=C*H*$_2$), 5.01 (1H, dd, J_{trans} 18.0, 1.5 Hz, -CH=C*H*$_2$), 3.65 (1H, q, *J* 2.5 Hz, -O-CH), 1.83-1.68 (6H, m), 1.52-1.19 (8H, m), 1.15-1.03 (2H, m); δ_C (75 MHz, $CDCl_3$) 142.8 (-*C*H=CH_2), 112.2 (-CH=*C*H$_2$), 72.0 (>*C*H-OH), 49.6 (2°), 43.1 (>*C*H-CH(OH)-), 39.5 (4°), 38.3 (2°), 33.9 (2°), 26.9 (2°), 25.6 (2°), 21.7 (2°), 16.6 (2°); ν_{max} (film) 3416, 2925, 2849, 1629, 1450, 12.43, 1153, 927, 903 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{20}O + H)^+$, 181.1592, found, 181.1583; $(C_{12}H_{20}O + Na)^+$, 203.1411, found, 203.1398.

Procedure B

To a solution of tosyl hydrazone **200** (0.720 g, 1.99 mmol, 1.00 equiv) in a mixture of Et_2O (20 mL) and THF (5mL) was added *n*-BuLi in hexanes (1.39 M, 4.42 mL, 6.15 mmol, 3.09 equiv), dropwise within 5 min at –78 °C. Then bright yellow reaction mixture was left to warm up to rt and the resulting orange solution then stirred under nitrogen atmosphere for 3.5 h. The reaction mixture then was washed with aq. NH_4Cl solution (3 × 20 mL), brine (20mL). The combined organic extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (10 to 20% EtOAc in petroleum ether) gave the title product **182** (0.25 g, 70%) as a colourless oil. Spectroscopic data correspond to those reported in procedure A.

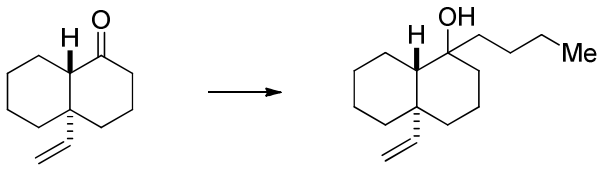
(4aR*,8aS*)-4a-Vinyldecahydronaphthalen-1-one (135)



182 **135**

This was performed by adaptation of a literature procedure.[156] To a stirred solution of oxalyl chloride (1.59 mL, 18.5 mmol, 1.10 equiv) in DCM (80 mL) at –78 °C under nitrogen was added dimethyl sulfoxide (2.57 mL, 36.2 mmol, 2.15 equiv). The solution was stirred for 10 min, and then vinyl alcohol **182** (3.04 mg, 16.8 mmol, 1.00 equiv) in dry DCM (20 mL) was added. The reaction mixture was stirred for 90 min at –78 °C, and then Et_3N (11.83 mL, 84.31 mmol, 5.00 equiv) was added. After 15 min the solution was allowed to warm to rt over 30 min, then water (100 mL) was added and the reaction mixture was transferred to a separating funnel. The mixture extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL) and dried over $MgSO_4$, then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% EtOAc in petroleum ether) to give the title ketone **135** (2.98 g, 99%) as a pale yellow oil; R_f 0.58 (25% EtOAc-petroleum ether); δ_H (300 MHz, $CDCl_3$) 5.48 (1H, dd, *J* 18.0, 11.0 Hz, -C*H*=CH_2), 5.12 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 4.93 (1H, dd, J_{trans} 18.0, 1.0 Hz, -CH=CH_2), 2.29-2.23 (2H, m), 2.15 (1H, dd, *J* 12.0, 3.0 Hz) 1.87-1.59 (7H, m), 1.47-1.25 (4H, m), 1.25-1.05 (1H, m); δ_C (75 MHz, $CDCl_3$) 212.3 (>C=O), 140.6 (-*C*H=CH_2), 116.1 (-CH=*C*H_2), 57.0 (>*C*H-CO-), 46.1 (4°), 41.2 (2°), 39.9 (2°), 39.8 (2°), 25.5 (2°), 22.1 (2°), 21.4 (2°), 21.0 (2°); ν_{max} (film) 2931, 2851, 1708, 1638, 1449, 1366, 1311, 1206, 1089, 999, 918, 838 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{18}O + H)^+$, 179.1435, found, 179.1428; $(C_{12}H_{18}O + Na)^+$, 201.1255, found, 201.1246.

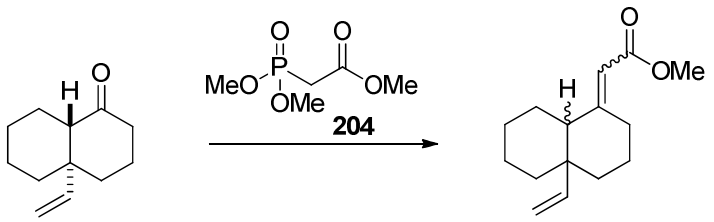
(4aR*,8aS*)-1-Butyl-4a-vinyldecahydronaphthalen-1-ol (203)



135 **203**

A stirred solution of phosphonoacetamide **169** (79.3 mg, 0.352 mmol, 1.00 equiv) in dry THF (10 mL) was treated with *n*-BuLi in hexanes (1.00 mL, 0.704 mmol, 2.00 equiv) at –78 °C and stirred for 10 min. Then ketone **135** (62.8 mg, 0.352 mmol, 1.00 equiv) in THF (10 mL) was added within 10 min and the resulting mixture was stirred for 1 h at –78 °C, then warmed up to rt and stirred for additional hour. The reaction mixture was then quenched by addition of a sat. NH_4Cl solution (20 mL), extracted with DCM (2 × 15 mL). The combined organic extracts were washed with water (2 × 10 mL) followed by brine (20 mL), then was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (5 to 20% EtOAc in petroleum ether) to give the title product **203** (0.714 g, 86%) single isomer as a colourless oil; R_f 0.58 (25% EtOAc-petroleum ether); δ_H (300 MHz, $CDCl_3$) 6.58 (1H, dd, *J* 18.0, 11.0 Hz, CH_2=C*H*-), 5.16 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 5.09 (1H, dd, J_{trans} 18.0, 1.5 Hz, -CH=CH_2), 1.93-1.04 (22H, m), 0.89 (3H, t, *J* 14.0 Hz, -CH_2-CH_3); δ_C (75 MHz, $CDCl_3$) 142.6 (-*C*H=CH_2), 112.7 (-CH=*C*H_2), 73.9 (>*C*(OH)-CH_2-CH_2-), 51.2 (>*C*H-C(OH)-CH_2-CH_2-), 44.5 (4°), 40.1 (2°), 39.9 (2°), 37.8 (2°), 37.2 (2°), 27.1 (2°), 25.9 (2°), 23.3 (2°), 21.7 (2°), 19.9 (2°), 17.6 (2°), 14.0 (1°); ν_{max} (film) 3474, 2924, 2852, 1454, 1378, 1282, 1147, 1005, 900 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{28}O + Na)^+$, 259.2037, found, 259.2014.

Methyl 2-(4a-vinyldecahydronaphthalen-1-ylidene)acetate (205)



135 **205**

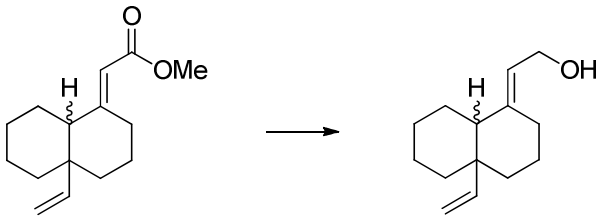
This was performed by adaptation of a literature procedure.[157] A solution *n*-BuLi in THF (1.81 M, 5.65 mmol, 1.68 equiv) was added to a solution of methyl 2-(dimethoxyphosphoryl)acetate **204** (0.990 mL, 6.93 mmol, 2.06 equiv) in dry THF (20 mL) at –78 °C and stirred for 30 min while temperature was left to rise to –10 °C. Then it was re-cooled to –78 °C and a solution of vinyl ketone **135** in THF was added dropwise. The resulting warmed up to rt within 1 h, then refluxed for 64 h. The reaction mixture was then quenched by careful addition of a sat. NH_4Cl solution and then extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL), then was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure then purified by column chromatography (5% EtOAc in petroleum ether) to give the title product as inseparable mixture of two epimers **205** (62.5 mg, 19%) as pale yellow oil; R_f 0.59 (10% EtOAc-petroleum ether):

Major epimer: δ_H (500 MHz, $CDCl_3$) 5.74 (1H, dd, *J* 18.0, 11.0 Hz CH_2=C*H*-), 5.48 (1H, s, >C=C*H*-CO_2CH_3), 5.12 (1H, d, J_{cis} 11.0 Hz, -CH=CH_2), 5.00 (1H, d, J_{trans} 18.0 Hz, -CH=CH_2), 3.95-3.91 (1H, m, >C*H*-C(4º)<), 3.68 (3H, s, =CH-CO_2CH_3), 1.99-1.95 (1H, m), 1.86-1.73 (3H, m), 1.66-1.21 (10H, m); δ_C (125 MHz, $CDCl_3$) 167.3 (>C=CH-*C*O_2CH_3), 164.5 >*C*=CH-CO_2CH_3), 141.0 (-*C*H=CH_2), 114.4 (-CH=*C*H_2), 112.0 (>C=*C*H-CO_2CH_3), 52.1 (1°), 50.8 (>*C*H-$C^{4°}$<), 44.6 (4°), 42.3 (2°), 40.0 (2°), 30.7 (2°), 26.4 (2°), 24.8 (2°), 23.4 (2°), 21.6 (2°); ν_{max} (film) 2927, 2857, 1716, 1638, 1433, 1385, 1208, 1165, 1137, 1025, 999, 913, 856, 732 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{15}H_{22}O_2 + H)^+$,

235.1698, found, 235.1677; calculated for $(C_{15}H_{22}O_2 + Na)^+$, 257.1517, found, 257.1506.

Minor epimer: δ_H (500 MHz, $CDCl_3$) 5.71 (1H, dd, *J* 17.0, 10.5 Hz CH_2=C*H*-), 5.65 (1H, s, >C=C*H*-CO_2CH_3), 4.96 (1H, d, J_{cis} 10.5 Hz, -CH=CH_2), 4.94 (1H, d, J_{trans} 17.0 Hz, -CH=CH_2), 3.67-3.66 (1H, m, >C*H*-C(4º)<), 3.65 (3H, s, =CH-CO_2CH_3), 2.12 (1H, dd, *J* 12.0, 4.0 Hz), 2.04 (2H, dq, *J* 13.5, 4.0 Hz), 1.82-1.19 (11H, m); δ_C (125 MHz, $CDCl_3$) 167.1 (>C=CH-*C*O_2CH_3), 166.0 >*C*=CH-CO_2CH_3), 147.6 (-*C*H=CH_2), 114.2 (-CH=*C*H_2), 112.1 (>C=*C*H-CO_2CH_3), 52.2 (1°), 50.7 (>*C*H-$C^{4°}$<), 41.1 (4°), 38.7 (2°), 38.0 (2°), 28.9 (2°), 25.9 (2°), 24.5 (2°), 22.3 (2°), 21.5 (2°); ν_{max} (film) 2927, 2857, 1716, 1638, 1433, 1385, 1208, 1165, 1137, 1025, 999, 913, 856, 732 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{15}H_{22}O_2 + H)^+$, 235.1698, found, 235.1677; calculated for $(C_{15}H_{22}O_2 + Na)^+$, 257.1517, found, 257.1506.

(E)-2-((4aR*,8aR*)-4a-Vinyldecahydronaphthalen-1-ylidene)ethanol (206)

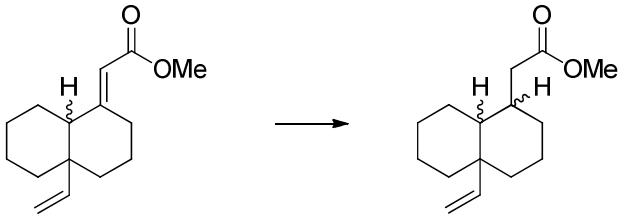


205 **206**

This was performed by adaptation of a literature procedure.[158] A solution of acetate **205** (45.0 mg, 0.192 mmol, 1.00 equiv) in THF (10 mL) was added to a suspension of $LiAlH_4$ in THF (7.28 mg, 0.192 mmol, 1.00 equiv) at –78 °C. The mixture was stirred for 1 h, then gradually warmed up to rt within 2 h and refluxed for 1.5 h. An extra equivalent of $LiAlH_4$ was added and refluxed for additional 30 min. Water was added with care until effervescence ceased, followed by aq. HCl (1.0 M) until all unreacted $LiAlH_4$ was dissolved. After extraction with ether (2 × 15 mL), the combined organic layers were dried with

$MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure Then purified by column chromatography (5 to 10% EtOAc in petroleum ether) to give the title product **206** (22.6 mg, 57%) as a pale yellow oil; R_f 0.19 (10% EtOAc-petroleum ether); δ_H (250 MHz, $CDCl_3$) 5.81 (1H, dd, *J* 18.0, 11.0 Hz, CH_2=C*H*-), 5.24 (1H, m, =C*H*-CH_2-OH), 5.08 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 4.99 (1H, dd, J_{trans} 18.0, 1.5 Hz, -CH=CH_2), 4.20 (2H, d, *J* 7.0 Hz, =CH-CH_2-OH), 2.71-2.64 (1H, m -CH_2-CH_2-C*H*<), 2.48-0.67 (19H, m); δ_C (62.5 MHz, $CDCl_3$) 144.6 (>*C*=CH-CH_2-OH), 141.8 (-*C*H=CH_2), 119.7 (>C=*C*H-CH_2-OH), 113.7 (-CH=*C*H_2), 58.9 (4°), 50.7 (=CH-*C*H_2-OH), 43.1 (3°), 42.6 (2°), 39.9 (2°), 29.6 (2°), 26.6 (2°), 24.9 (2°), 23.3 (2°), 21.8 (2°); ν_{max} (film) 3304, 2924, 2852, 1450, 999, 909 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{14}H_{22}O + H)^+$, 207.1743, found, 207.1735; calculated for $(C_{14}H_{22}O + Na)^+$, 229.1563, found, 229.1554.

Methyl 2-(4a-vinyldecahydronaphthalen-1-yl)acetate (207)

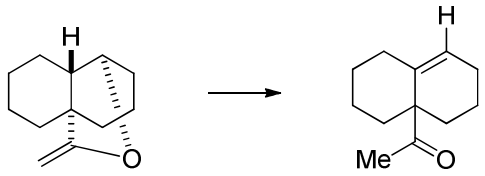


205 **207**

This was performed by adaptation of a literature procedure.[72] A mixture of **205** (67.5 mg, 0.288 mmol, 1.00 equiv) and dry MeOH (5 mL) under N_2 atmosphere was stirred at rt for 3 h. the resulting mixture was quenched by careful addition of aq HCl (1.00 M, 10 mL) until excess Mg dissolved. The reaction mixture was extracted with ether (2 × 10 mL), and then the combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give a mixture of four inseparable diastereomers **207** (60.0 mg, 88%) as an oil; R_f 0.45 (5% EtOAc-petroleum

ether); TOF-ESI+ *m/z* calculated for $(C_{15}H_{24}O_2 + H)^+$, 259.1674, found, 259.1648.

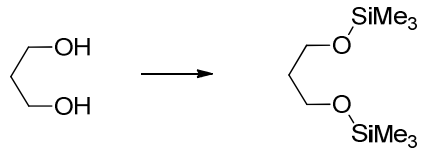
1-(1,2,3,4,4a,5,6,7-Octahydronaphthalen-4a-yl)ethanone (232)



176 **232**

This was performed by adaptation of a literature procedure.[80] To a stirring solution of vinyl ether **176** (16.3 g, 91.3 mmol, 1.00 equiv) in DCM was added ethylene glycol (13.3 g, 215 mmol, 2.35 equiv) followed by a substoichiometric amount of *p*-TSA. The mixture was then refluxed for 15 h using a Dean–Stark trap. The reaction mixture was then washed with sat. aq. $NaHCO_3$ solution (2 × 25 mL), water (25 mL) and brine (25 mL). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the title product **232** (11.8 g, 66%) as a colourless oil; R_f 0.45 (10% EtOAc-petroleum ether); δ_H (300 MHz, $CDCl_3$) 6.57 (1H, dt, *J* 1.5, 1.0 Hz, =C*H*-), 2.21-2.05 (2H, m), 2.06 (3H, m, -CH_3), 1.98-1.85 (3H, m), 1.77-1.15 (9H, m); δ_C (75 MHz, $CDCl_3$) 212.4 (>*C*=O), 138.8 (>*C*=CH-), 122.7 (>C=*C*H-), 54.4 (4°), 36.6 (2°), 34.6 (2°), 34.5 (2°), 27.7 (2°), 25.3 (2°), 25.1 (>CO-*C*H_3), 23.6 (2°), 19.0 (2°); ν_{max} (film) 2926, 2855, 1701, 1662, 1445, 1349, 1150, 1090, 999, 809 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{18}O + H)^+$, 179.1435, found, 179.1438; calculated for $(C_{12}H_{18}O + Na)^+$, 201.1255, found, 201.1260.

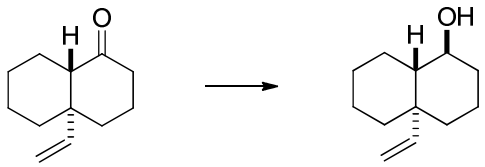
1,3-Bis(trimethylsilyloxy) propane (234)



234

This was performed by adaptation of a literature procedure.[159] To a solution of propane-1,3-diol (15.0 g, 0.197 mol, 1.00 equiv), and DMAP (2.40 g, 10 mol%) in DMF (250 mL) at 0 °C was added trimethylsilyl chloride (56.0 mL, 0.443 mol, 2.25 equiv). The reaction mixture was stirred for 30 min. Then Et_3N (110 mL, 0.788 mol, 4.00 equiv) was added and the resulting reaction mixture was left to stir for 18 h. The reaction mixture was then washed with water (3 × 500 mL), extracted with DCM (3 × 150 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by distillation to afford the title compound **234** (34.7 g, 80%) as a colourless liquid; (b.pt. 36–38 °C at 1.2 Torr). Analytical data were consistent with those previously reported:[160] δ_H (300 MHz, $CDCl_3$) 3.65 (4H, t, *J* 6.5 Hz, -CH_2-C*H*$_2$-OSi$(CH_3)_3$)), 1.73 (2H, d, *J* 6.5 Hz, -C*H*$_2$-CH_2-OSi$(CH_3)_3$)), 0.10 (18H, s, -CH_2-OSi$(CH_3)_3$)). δ_C (75 MHz, $CDCl_3$) 59.1 (-CH_2-*C*H_2-O-Si$(CH_3)_3$)), 35.5 (-*C*H_2-CH_2-O-Si$(CH_3)_3$)), -0.5 (-CH_2-O-Si(*C*$H_3)_3$).

(1S*,4aR*,8aS*)-4a-Vinyldecahydronaphthalen-1-ol (248)



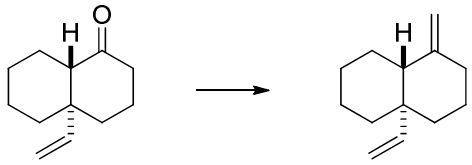
135 **248**

This was performed by adaptation of a literature procedure.[161] To a stirred solution of vinyl ketone **135** (0.580 g, 3.25 mmol, 1.00 equiv) in anhydrous THF (30 mL), was added 9-BBN (0.500 M in THF, 9.76 mL, 4.88 mmol, 1.50 equiv) dropwise at 0 °C and the resulting mixture was then stirred at rt for 4 h. H_2O (1 mL) was added followed by aq. NaOH (3.00 M, 8 mL) and aq. 30% H_2O_2 (6 mL). The reaction mixture was heated to 60 °C and stirred for 2 h, then extracted with EtOAc (2 × 15 mL). The combined extracts were washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Purification by column chromatography (25% EtOAc in petroleum ether) gave two diastereomers:

The major diastereomer was alcohol **182** (210 mg, 35%) as colourless oil. Spectroscopic data correspond to those already reported (*vide supra*).

The minor diastereomer was the title alcohol **248** (61.4 mg, 11%), a white solid; m.pt. 54–56 °C; R_f 0.46 (30% EtOAc in petroleum ether); δ_H (250 MHz, $CDCl_3$) 6.00 (1H, dd, *J* 18.0, 11.5 Hz, C*H*-CH_2), 5.16 (1H, dd, J_{cis} 11.5, 0.5 Hz, -CH=CH_2), 5.01 (1H, dd, J_{trans} 18.0, 1.0 Hz, -CH=CH_2), 3.44 (1H, td, *J* 10.5, 4.5 Hz, HO-CH<), 2.01-1.03 (16H, m); δ_C (62.5 MHz, $CDCl_3$) 142.0 (-*C*H=CH_2), 114.1 (-CH=*C*H_2), 70.4 (>*C*H-OH), 52.9 (2°), 41.6 (3°), 41.5 (4°), 40.0 (2°), 36.5 (2°), 26.4 (2°), 22.8 (2°), 21.8 (2°), 20.3 (2°); ν_{max} (film) 3416, 2925, 2849, 1629, 1450, 1243, 1153, 927, 903 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{20}O + H)^+$, 181.1592, found, 181.1583; $(C_{12}H_{20}O + Na)^+$, 203.1411, found, 203.1398.

(4aR*,8aR*)-1-Methylene-4a-vinyldecahydronaphthalene (250)



135 **250**

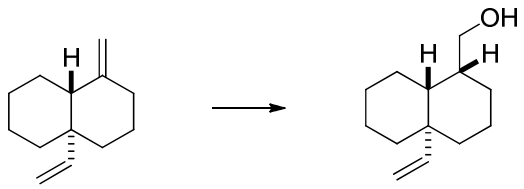
Procedure A

This was performed by adaptation of a literature procedure.[162] A solution of methyltriphenylphosphonium bromide (25.0 g, 70.1 mmol, 2.50 equiv) and potassium *tert*-butoxide (1.00 M in THF, 56.0 mL, 56.0 mmol, 2.00 equiv) in THF (150 mL) was stirred at reflux for 3 h. Vinyl ketone **135** (5.00 g, 28.0 mmol, 1.00 equiv) in toluene (15 mL) was then added dropwise to the above solution and the resulting mixture was stirred at reflux for 16 h. The reaction was carefully quenched by the addition of acetone (100 mL) and stirred at 60 °C for 30 min. The reaction mixture was then allowed to cool to rt and water (100 mL) was added. The reaction mixture was extracted with Et_2O (3 × 120 mL) and the combined organic layers were washed with brine (2 × 150 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (100% hexane) gave the title alkene **250** (4.55 g, 92%) as a colourless liquid; b.pt. 233–235 °C at 760 Torr; R_f 0.73 (100% pentane); δ_H (500 MHz, $CDCl_3$) 5.86 (1H, dd, *J* 18.0, 11.0 Hz, CH_2=C*H*-), 5.13 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 5.01 (1H, dd, J_{trans} 18.0, 1.5 Hz, -CH=CH_2), 4.76 (1H, q, *J* 1.5 Hz, >C=CH_2), 4.52 (1H, q, *J* 1.5 Hz, >C=CH_2), 2.37-2.28 (1H, m), 2.11-1.99 (1H, m), 1.86-1.74 (3H, m), 1.65-1.18 (10H, m); δ_C (125 MHz, $CDCl_3$) 150.6 (>*C*=CH_2), 142.1 (-*C*H=CH_2), 113.6 (-CH=*C*H_2), 106.1 (>C=*C*H_2), 50.2 (4°), 42.7 (2°), 42.6 (3°), 39.6 (2°), 36.9 (2°), 26.7 (2°), 25.1 (2°), 23.5 (2°), 21.9 (2°); ν_{max} (film) 2926, 2845, 1644, 1145, 1140, 1230, 1151, 997, 858, 785 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{13}H_{20} + H)^+$, 177.1638, found, 177.1634.

Procedure B

This was performed in accordance with a literature procedure.[163] To a stirred solution of methyltriphenylphosphonium bromide (15.5 g, 43.5 mmol, 2.25 equiv) in dry THF (100 mL) at 0 °C, *n*-BuLi (1.41M, 20.5 mL, 29.0 mmol, 1.50 equiv) was added dropwise. The reaction mixture was left to warm up to rt and stirred for 2.5 h. The mixture was then cooled to –78 °C and vinyl ketone **135** (3.45 g, 19.3 mmol, 1.00 equiv) in THF (20 mL) was then added dropwise over 15 min. The resulting solution was stirred at the same temperature for 1 h before being allowed to warm to rt and stirred for 18 h. The reaction was quenched by addition of aq. NH_4Cl solution (100 mL). The reaction mixture was extracted with Et_2O (3 × 120 mL); the combined organic layers were washed with brine (2 × 100 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure then purified by column chromatography (100% petroleum ether to 10% EtOAc in petroleum ether) to give the desired bis(alkene) **250** (2.46 g, 72%) as a colourless liquid. Spectroscopic data correspond to those reported in procedure A.

((1R*,4aR*,8aR*)-4a-Vinyldecahydronaphthalen-1-yl)methanol (249)

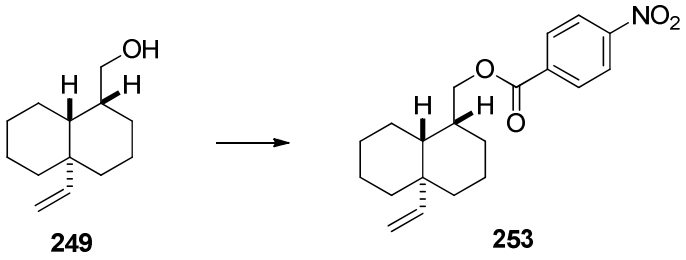


250 **249**

This was performed by adaptation of a literature procedure.[162] To a stirred solution of bis(alkene) **250** (2.35 g, 13.3 mmol, 1.00 equiv) in anhydrous THF (75 mL) was added 9-BBN (0.5 M THF solution, 39.9 mL, 20.0 mmol, 1.50 equiv) dropwise at –15 °C and the resulting mixture was stirred for 15 min. The reaction mixture was allowed to warm up to rt and stirred for 120 h. Aq. NaOH (3.00 M, 30 mL) followed by aq. 30% H_2O_2 (30 mL) was added. The resulting

exothermic reaction was left to cool to rt with stirring over 3 h. The reaction mixture was then diluted with aq. NH_4Cl (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (2 × 25 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (25% EtOAc in petroleum ether) gave the title alcohol **249** (2.20 g, 85%) as a colourless oil; R_f 0.39 (25% EtOAc in petroleum ether); δ_H (250 MHz, $CDCl_3$) 6.09 (1H, dd, *J* 16.5, 10.5 Hz, -C*H*-CH_2), 5.05 (1H, dd, J_{cis} 10.5, 1.5 Hz, -CH=CH_2), 4.99 (1H, dd, J_{trans} 16.5, 1.5 Hz, -CH=CH_2), 3.66-3.56 (2H, m, -CH_2-OH), 1.93-1.01 (17H, m); δ_C (62.5 MHz, $CDCl_3$) 142.6 (-*C*H=CH_2), 112.1 (-CH=*C*H_2), 60.8 (>CH-*C*H_2-OH), 48.2 (>*C*H-CH_2-OH), 45.0 (>*C*H-CH-CH_2-OH), 43.1 (2°), 40.6 (4°), 38.5 (2°), 28.1 (2°), 27.5 (2°), 26.6 (2°), 22.1 (2°), 17.5 (2°); ν_{max} (film) 3311, 2923, 2859, 1631, 1448, 1410, 1223, 1149, 1069, 1020, 995, 974, 847 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{13}H_{22}O + H)^+$, 195.1748, found, 195.1729.

((1R,4aR*,8aR*)-4a-Vinyldecahydronaphthalen-1-yl)methyl 4-nitrobenzoate (253)*

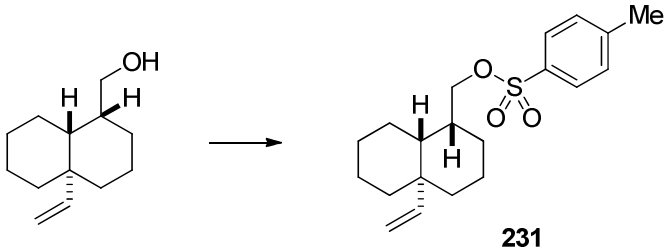


249 **253**

This was performed by adaptation of a literature procedure.[164] To a stirred solution of alcohol **249** (40.0 mg, 0.208 mmol, 1.00 equiv) in anhydrous DCM (10 mL), were added 4-nitrobenzoyl chloride (38.1 mg, 0.208 mmol, 1.00 equiv), pyridine (32.0 mg, 33.0 µL, 0.411 mmol, 2.00 equiv), and catalytic amounts of DMAP (2.5 mg, 10 mol%). Resulting reaction mixture was stirred at rt for 6 h. After completion of reaction, the reaction mixture was quenched by addition of

aq. NaOH (0.500 M, 5 mL) and extracted with DCM (2 × 20 mL). The combined extracts were washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (20% EtOAc in petroleum ether) gave the title ester **253** (40.6 mg, 58%) as pale yellow solid, m.pt. 69–71 °C; R_f 0.65 (25% EtOAc in petroleum ether); δ_H (250 MHz, $CDCl_3$) 8.20 (2H, d, *J* 9.0 Hz, Ar-*H*), 8.11 (2H, d, *J* 9.0 Hz, Ar-*H*) 6.22 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*=CH_2), 5.15 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 5.08 (1H, dd, J_{trans} 17.5, 1.5 Hz, -CH=CH_2), 4.39 (2H, d, *J* 7.5 Hz, >CH-CH_2-O-), 2.01-1.06 (14H, m), 0.91-0.71 (2H, m); δ_C (62.5 MHz, $CDCl_3$) 164.7 (>C=O), 150.4 (Ar-*C*-NO_2), 141.9 (-*C*H=CH_2), 135.9 (Ar-*C*-CO_2-), 130.5 (Ar-*C*H-), 123.4 (Ar-*C*H), 112.9 (-CH=*C*H_2), 64.8 (>CH-*C*H_2-O-), 48.0 (3°), 45.0 (4°), 40.0 (2°), 39.2 (2°), 38.1 (2°), 28.8 (2°), 27.5 (2°), 26.6 (2°), 22.0 (2°), 17.4 (2°); ν_{max} (film) 2925, 2853, 1721, 1608, 1527, 1449, 1345, 1270, 1116, 1014, 952, 913 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{20}H_{25}NO_4 + H)^+$, 344.1854, found, 344.1843.

((1R,4aR*,8aR*)-4a-Vinyldecahydronaphthalen-1-yl)methyl 4-methylbenzenesulfonate (231)*

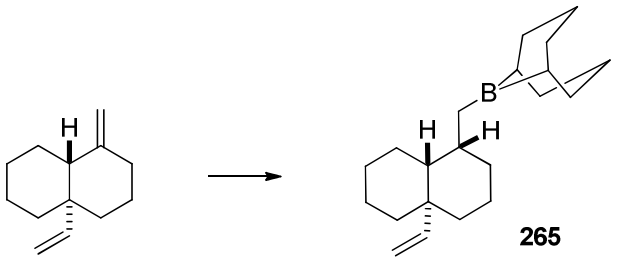


249 **231**

To a mixture of the alcohol **249** (215 mg, 1.10 mmol, 1.00 equiv) and DMAP (1.3 mg, 10 mol%) in anhydrous DCM (10 mL) was added *p*-toluenesulfonylchloride (316 mg, 1.65 mmol, 1.50 equiv) and Et_3N (0.610 mL, 4.42 mmol, 4.00 equiv) at 0 °C. The resulting mixture was allowed to warm up to rt stirred for 16 h. The reaction mixture then was diluted with DCM (15 mL),

washed with water (2 × 20 mL), aq. $NaHCO_3$ (2 × 15 mL), brine (2 × 20 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (10 to 20% EtOAc in petroleum ether) to give the title product **231** as pale yellow oil (244 mg, 68%); R_f 0.48 (15% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.0 Hz, Ar-*H*), 7.32 (2H, d, *J* 8.0 Hz, Ar-*H*), 5.98 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*-CH_2), 5.00 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 4.92 (1H, dd, J_{trans} 17.5, 1.5 Hz, -CH=CH_2), 4.10-3.96 (2H, m, >CH-CH_2-O-), 2.43 (3H, s, -CH_3), 1.87-0.64 (16 H, m); δ_C (75 MHz, $CDCl_3$) 144.6 (Ar >*C*-SO_2-), 141.5 (-*C*H=CH_2), 133.1 (Ar >*C*-CH_3), 129.6 (Ar -*C*H-), 127.8 (Ar -*C*H-), 112.8 (-CH=*C*H_2), 69.5 (>CH-*C*H_2-O-), 47.6 (3°), 44.8 (2°), 39.7 (2°), 39.1 (4°), 37.6 (3°), 28.0 (2°), 27.3 (2°), 26.2 (2°), 21.8 (2°), 21.5 (1°), 16.95 (2°); ν_{max} (film) 2926, 2859, 1632, 1495, 1449, 1358, 1174, 1097, 950, 839, 812 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{20}H_{28}SO_3 + Na)^+$, 371.1656, found, 371.1644.

9-(((1R,4aR*,8aR*)-4a-Vinyldecahydronaphthalen-1-yl)methyl)-9-borabicyclo[3.3.1]nonane (265)*



250 **265**

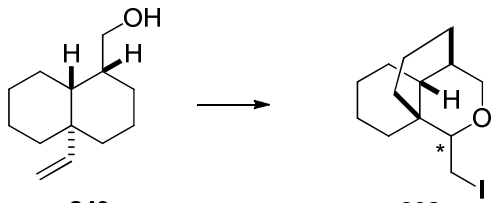
This was performed by adaptation of a literature procedure.[162] To a stirred solution of bis(alkene) **250** (3.95 g, 22.4 mmol, 1.00 equiv) in anhydrous THF (80 mL), 0.500 M THF solution of 9-BBN (67.2 mL, 33.6 mmol, 1.50 equiv) was added dropwise at 0 °C. The resulting mixture was allowed to warm up to rt and stirred for 72 h. Aq. NaOH (3.00 M, 25 mL) following by aq. 30% H_2O_2 (25 mL) was added, resulting in an exotherm. The reaction mixture was left to cool to rt

with stirring over 1 h. The reaction mixture was then diluted with aq. NH_4Cl (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (100 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (25% EtOAc in petroleum ether) gave two products:

The major product was the alcohol **249** (2.98 g, 69%), a colourless oil. Spectroscopic data correspond to those already reported (*vide supra*).

The minor product was the title borane **265** (0.96 g, 14%), a colourless oil; R_f 0.65 (20% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 6.27 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*-CH_2), 5.01 (1H, dd, J_{cis} 11.0, 1.5 Hz, -CH=CH_2), 4.96 (1H, dd, J_{trans} 17.5, 1.5 Hz, -CH=CH_2), 2.14-0.80 (31H, m); δ_C (75 MHz, $CDCl_3$) 142.7 (-*C*H=CH_2), 111.4 (-CH=*C*H_2), 75.6 (>CH-*C*H_2-B<), 49.5 (2°), 44.4 (4°), 40.3 (3°), 39.1 (2°), 38.4 (3°), 36.6 (3°), 35.8 (3°), 33.8 (2°), 32.8 (2°), 28.2 (2°), 28.2 (2°), 27.3 (2°), 27.1 (2°), 24.8 (2°), 22.2 (2°), 22.2 (2°), 22.0 (2°), 17.6 (2°); ν_{max} (film) 2918, 2850, 1632, 1447, 1380, 1215,1096, 1013, 957, 848, 754 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{31}H_{35}B + H)^+$, 299.2904, found, 299.2899.

(((1R,4aS*)-Decahydro-1,4a-methanooxymethanonaphthalen-9-yl)methyl) iodide (262)*



249 **262**

Procedure A

This was performed by adaptation of a literature procedure.[91] To a solution of ethylenebis(diphenylphosphine) (1.01 g, 2.54 mmol, 1.10 equiv) in DCM (25

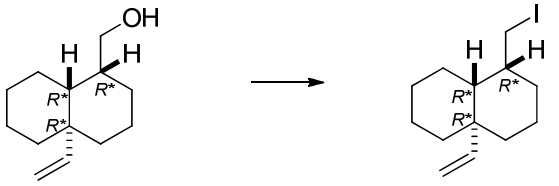
mL), 1,2-diiodoethane (1.43 g, 5.09 mmol, 2.20 equiv) was added in one portion at 0 °C and stirred. Reaction temperature was kept below 10 °C for 15 min. The solution of alcohol **249** (0.45 g, 2.31 mmol, 1.00 equiv) in DCM (10 mL) was then added dropwise to the yellow reagent mixture. After addition of all substrate, resulting reaction mixture was stirred at reflux for 16 h before concentrating it under reduced pressure. To this brown residue was added K_2CO_3 (1.25 g), diluted with Et_2O (50 mL) and added water (25 drops). The mixture then was stirred at rt for 30 min. Additional K_2CO_3 was added to dry the solution. The solids were washed with ether (2 × 20 mL), combined organic layers were concentrated to give the crude. Purified by column chromatography (5% to 20% EtOAc in petroleum ether) to give the title product **262** (350 mg, 47%) as a single isomer and colourless oil; R_f 0.36 (5% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 4.16 (1H, m, >C*H*-CH_2-I), 4.01 (1H, dt, *J* 11.0, 2.0 Hz, >CH-C*H*$_2$-O-CH<), 3.57 (1H, d, *J* 11.5 Hz, >CH-C*H*$_2$-O-CH<), 2.33-2.17 (1H, m, >C*H*-CH_2-O-CH<), 1.99-1.55 (5H, m), 1.50-1.20 (8H, m), 1.08 (2H, d, *J* 6.5 Hz, >CH-C*H*$_2$-I), 0.91 (1H, tdd, *J* 13.5, 6.0, 1.5 Hz), 0.81-0.78 (1H, m); δ_C (75 MHz, $CDCl_3$) 71.4 (>*C*H-CH_2-I), 67.9 (>CH-*C*H_2-O-CH<), 44.6 (>*C*H-CH<), 37.0 (>*C*H-CH_2-O-CH<), 36.9 (4°), 35.8 (2°), 35.0 (2°), 33.3 (2°), 26.8 (2°), 25.7 (2°), 22.4 (2°), 21.7 (2°), 15.1 (>CH-*C*H_2-I); ν_{max} (film) 2924, 2854, 1460, 1377, 1259, 1076, 1017, 798, 752, 606 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{13}H_{21}IO + H)^+$, 321.0717, found, 321.0714.

Procedure B

This was performed by adaptation of a literature procedure.[91] A solution of iodine (261 mg, 1.02 mmol, 2.00 equiv) in DCM (5 mL) was added dropwise to a stirred solution of ethylenebis(diphenylphosphine) (256 mg, 0.640 mmol, 1.25 equiv) in DCM (5 mL) at 0 °C. Reaction temperature was kept below 10 °C for 30 min. The solution of alcohol **249** (100 mg, 0.510 mmol, 1.00 equiv) in DCM (5 mL) was then added dropwise to the reagent mixture. After addition of all substrate, resulting reaction mixture was stirred at the rt for 16 h. Then reaction solvent was removed under reduced pressure, the residue was diluted with

Et_2O (25 mL), washed with aq. solution of $Na_2S_2O_3$ (2 × 15 mL). Combined organic extracts were then washed with brine (25 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography to afford the title product **262** (30.0 mg, 18%) as a colourless oil. Spectroscopic data correspond to those reported in procedure A.

((1R*,4aR*,8aR*)-4a-Vinyldecahydronaphthalen-1-yl)methyl iodide (260)

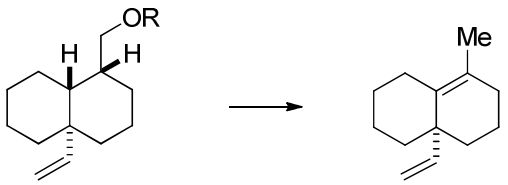


249 **260**

This was performed by adaptation of a literature procedure.[91] A solution of iodine (520 mg, 2.05 mmol, 2.00 equiv) in DCM (10 mL) was added dropwise to a stirred solution of ethylenebis(diphenylphosphine) (1.23 g, 3.08 mmol, 3.00 equiv) in DCM (5 mL) at 0 °C. Reaction temperature was kept below 10 °C for 30 min. The solution of alcohol **249** (200 mg, 1.02 mmol, 1.00 equiv) in DCM (5 mL) was then added dropwise to the reagent mixture within 20 min. After addition of all substrate, resulting reaction mixture was stirred at the rt for an additional hour before refluxing it for 18 h. Then reaction solvent was removed under reduced pressure, the residue was washed with pentane (3 × 15 mL). Combined filtrates were concentrated under reduced pressure and again washed with pentane. This washing procedure was repeated 5 times to give the title product **260** (190 mg, 61%) a colourless oil; δ_H (300 MHz, $CDCl_3$) 5.54 (1H, dd, *J* 17.5, 10.5 Hz, C*H*=CH_2), 5.12 (1H, dd, J_{cis} 10.5, 2.0 Hz, -CH=CH_2), 4.79 (1H, dd, J_{trans} 17.5, 2.0 Hz, -CH=CH_2), 2.54-2.46 (1H, m), 2.36-2.27 (1H, m), 2.24-0.99 (16H, m); δ_C (75 MHz, $CDCl_3$) 142.7 (-*C*H=CH_2), 114.1 (-CH=*C*H_2), 49.5 (3°), 41.8 (4°), 40.6 (2°), 36.7 (2°), 34.0 (2°), 29.6 (2°), 26.6 (2°), 23.8 (2°), 21.7 (2°), 21.0 (3°), 18.1 (>CH-*C*H_2-I); ν_{max} (film) 3311, 2923, 2859, 1631, 1448,

1410, 1223, 1149, 1069, 1020, 995, 974, 847 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{13}H_{21}I - HI + H)^+$, 177.1638, found, 177.1634.

1-Methyl-4a-vinyl-2,3,4,4a,5,6,7,8-octahydronaphthalene (261)



R = H, **249**
Ts, **231**

261

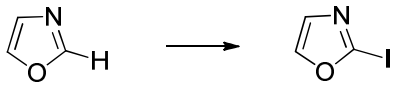
Procedure A

This was performed by adaptation of a literature procedure.[165] To a solution of vinyl alcohol **249** (200 mg, 1.02 mmol, 1.00 equiv) in DCM (10 mL) was added PPh_3 (539 mg, 2.05 mmol, 2.00 equiv) and CBr_4 (683 mg, 2.05 mmol, 2.00 equiv) at 0 °C and the mixture was stirred for 18 h. Sat. aq. $NaHCO_3$ (15 mL) was added to the mixture followed by addition of EtOAc (30 mL). The organic layer was separated, and aqueous phase was further extracted with EtOAc (2 ×25 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (5% to 20% EtOAc in petroleum ether) to give the title product **261** (70.0 mg, 32%) as a colourless oil; R_f 0.76 (10% EtOAc-petroleum ether); δ_H (250 MHz, $CDCl_3$) 5.54 (1H, dd, *J* 17.5, 10.5 Hz, -C*H*=CH_2), 5.11 (1H, dd, J_{cis} 10.5, 2.0 Hz, -CH=CH_2), 4.79 (1H, dd, J_{trans} 17.0, 2.0 Hz, -CH=CH_2), 2.53-2.45 (1H, m), 2.08-1.68 (5H, m), 1.65 (3H, s, -CH_3), 1.59-1.10 (8H, m); δ_C (62.5 MHz, $CDCl_3$) 146.4 (-*C*H=CH_2), 131.7 (4°), 126.9 ((=*C*(CH_3)-), 4°), 115.2 (-CH=*C*H_2), 43.1 (4°), 41.7 (2°), 37.8 (2°), 32.9 (2°), 27.8 (2°), 25.9 (2°), 23.1 (2°), 19.1 (2°), 17.8 (1°); ν_{max} (film) 2924, 2853, 1633, 1446, 1401, 1148, 996, 914 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{13}H_{20} + H)^+$, 177.1643, found, 177.1635.

Procedure B

This was performed by adaptation of a literature procedure.[166] To a solution containing of vinyl tosylate **231** (105 mg, 0.300 mmol, 1.00 equiv) in NaI sat. acetone (10 mL) was refluxed for 72 h. The cooled reaction mixture was diluted with Et_2O (30 mL) washed with sat. aq. $Na_2S_2O_3$ (20 mL), brine (2 × 20 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated to give the crude product. Purification by column chromatography (5% to 10% EtOAc in petroleum ether) gave the title product **261** (28.2 mg, 53%) as a colourless oil. Spectroscopic data correspond to those reported in procedure A.

2-Iodooxazole (264)[94]



213 **264**

Procedure A

This was performed in accordance with a literature procedure.[94] *n*-BuLi (2.50 M in hexanes, 2.89 mL, 7.24 mmol, 1.00 equiv) was added to a solution of $MgBr_2$ (0.440 g, 2.39 mmol 0.33 equiv) in THF (5 mL) cooled to –10 °C. After stirring for 1 h, oxazole **213** (0.470 mL, 7.24 mmol, 1.00 equiv) was introduced. The reaction mixture allowed to warm up to rt and stirred for 2 h before solution of iodine (1.83 g, 7.24 mmol, 1.00 equiv) in THF (3 mL) was introduced. The reaction was stirred for 18 h, and then quenched by addition of sat. aq. $Na_2S_2O_3$ solution (25 mL) until no iodine colour persisted. The reaction mixture was extracted with chloroform (3 × 20 mL), and the combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in DCM (20 mL) and filtered through a short pad of silica gel, then concentrated under reduced pressure to give 2-iodooxazole **264** (110 mg, 8%) as a pale yellow

solid. Analytical data were consistent with those previously reported:[94] δ_H (300 MHz, $CDCl_3$) 7.77 (1H, s), 7.10 (1H, s); δ_C (75 MHz, $CDCl_3$) 144.8, 129.8, 101.3.

Procedure B

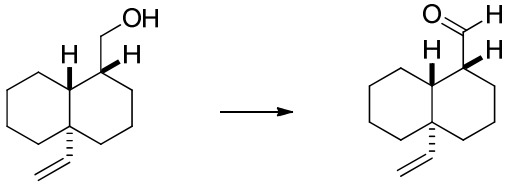
This was performed by adaptation of a literature procedure.[96] To a solution of oxazole **213** (500 mg, 0.470 mL, 7.24 mmol 1.00 equiv) in THF (20 mL) at –78 °C was added *n*-BuLi (2.20 M in hexanes, 3.62 mL, 7.96 mmol, 1.10 equiv) dropwise over 15 min. Reaction mixture was stirred at the temperature for 1 h before a solution of 1,2-diiodoethane (2.24 g, 7.96 mmol, 1.10 equiv) in Et_2O (10 mL) was added and resulting mixture allowed to warm up to rt. After 1 h, the reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ solution (30 mL), extracted with Et_2O (3 × 20 mL) and combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give 2-iodooxazole **264** (660 mg, 47%) as a pale yellow solid. Spectroscopic data correspond to those reported in procedure A.

Procedure C

This was performed in accordance with a literature procedure.[97] To a solution of oxazole **213** (500 mg, 0.470 mL, 7.24 mmol 1.00 equiv) in THF (10 mL) cooled to –78 °C was added *n*-BuLi (2.20 M in hexanes, 3.62 mL, 7.96 mmol, 1.10 equiv) dropwise over 15 min. Reaction mixture was stirred at the temperature for 1 h. Then a solution of anhydrous $ZnCl_2$ in Et_2O (3.00 M, 8.00 mL, 24.2 mmol, 6.00 equiv) was added dropwise over 5 min. The reaction mixture allowed to warm up to rt and stirred for 1 h before adding a solution of iodine (2.02 g, 7.96 mmol, 1.10 equiv) in THF (10 mL) in one portion. The resulting mixture was stirred for 30 min, quenched by addition of sat. aq. $Na_2S_2O_3$ solution (25 mL), diluted with Et_2O (50 mL) and poured into aq. citric acid solution (10 wt%, 50 mL). The biphasic mixture was vigorously stirred for 15 min before clean separation of layers occurred and separated. The organic layer

was washed with brine (50 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in DCM (20 mL) and filtered through a short pad of silica gel, then concentrated under reduced pressure to give 2-iodooxazole **264** (800 mg, 57%) as a pale yellow solid. Spectroscopic data correspond to those reported in procedure A.

(1R*,4aR*,8aR*)-4a-Vinyldecahydronaphthalene-1-carbaldehyde (223)



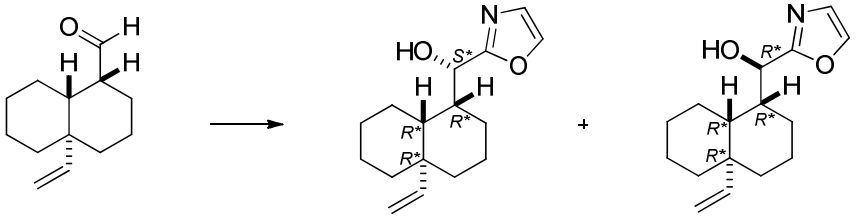
249 **223**

This was performed by adaptation of a literature procedure.[156] To a stirred solution of oxalyl chloride (1.38 mL, 16.1 mmol, 1.10 equiv) in DCM (80 mL) at –78 °C was added DMSO (2.23 mL, 31.5 mmol, 2.15 equiv). The solution was stirred for 20 min, and then alcohol **249** (2.85 g, 14.7 mmol, 1.00 equiv) in dry DCM (20 mL) was added. The reaction mixture was stirred at –78 °C under nitrogen for 2.5 h, and then Et_3N (10.3 mL, 73.3 mmol, 5.00 equiv) was added at the same temperature. After 20 min the solution allowed to warm to rt over 30 min, then water (100 mL) was added and the reaction mixture was extracted with Et_2O (2 × 75 mL). The combined organic extracts were washed with brine (2 × 50 mL) and dried over $MgSO_4$, then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (10% EtOAc in petroleum ether) to give the title aldehyde **223** (2.45 g, 87%) as a pale yellow oil; R_f 0.64 (20% EtOAc-petroleum ether); δ_H (400 MHz, $CDCl_3$) 9.89 (1H, s, -CHO), 5.99 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*=CH_2), 5.14 (1H, d, J_{cis} 11.0 Hz, -CH=CH_2), 5.06 (1H, d, J_{trans} 17.5 Hz, -CH=CH_2), 2.23-2.19 (2H, m), 1.98-0.66 (14H, m); δ_C (100 MHz, $CDCl_3$) 204.7 (>CH-*C*HO), 140.2 (-*C*H=CH_2), 115.1 (-CH=*C*H_2), 51.9 (3°), 48.2 (3°), 43.0 (2°), 40.6 (4°), 38.8 (2°), 27.5 (2°), 26.4 (2°),

26.0 (2°), 21.9 (2°), 18.6 (2°); ν_{max} (film) 2923, 2854, 1723, 1448, 1236, 1074, 911 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{12}H_{20}O + H)^+$, 193.1593, found, 193.1587; $(C_{12}H_{20}O + Na)^+$, 215.1413, found, 215.1404.

(S*)-Oxazol-2-yl((1R*,4aR*,8aR*)-4a-vinyldecahydronaphthalen-1-yl)methanol (266)

(R*)-Oxazol-2-yl((1R*,4aR*,8aR*)-4a-vinyldecahydronaphthalen-1-yl)methanol (267)



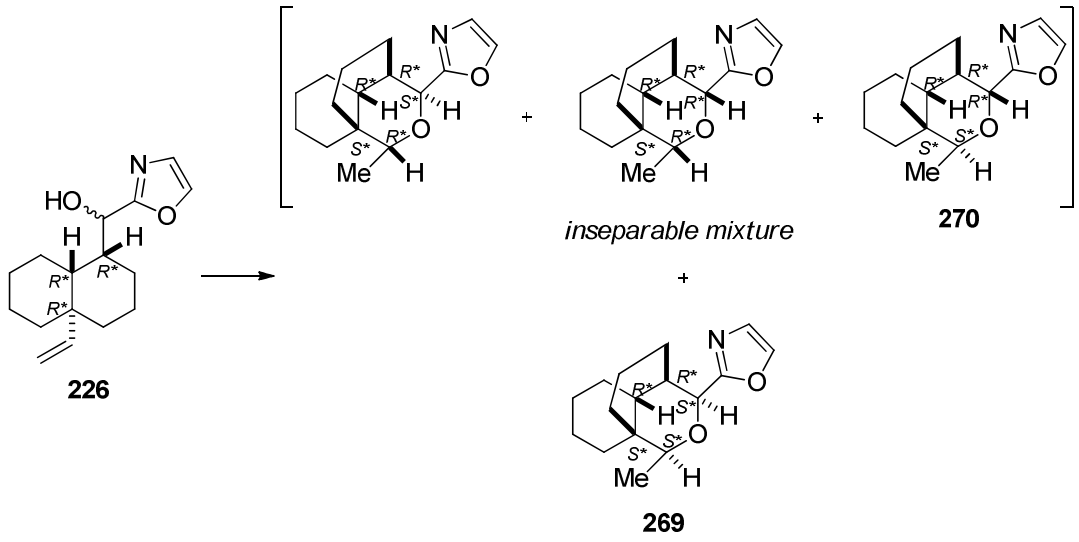
This was performed by adaptation of a literature procedure.[88,167] To a solution of oxazole **213** (355 mg, 338 µL, 5.14 mmol, 1.00 equiv) in anhydrous THF (15 ml), in a flame dried flask, BH_3·THF complex (1.00 M in THF, 5.40 mL, 5.40 mmol, 1.05 equiv) was added at rt. After being stirred at rt for 1 h, the colourless solution was cooled to –78 °C and *n*-BuLi in hexanes (1.50 M, 3.60 mL, 5.40 mmol, 1.05 equiv) was added dropwise over 15 min. The resulting yellow solution was stirred at –78 °C for 90 min before a solution of aldehyde **223** (0.990 g, 5.14 mmol, 1.00 equiv) in THF (15 mL) was added dropwise over 30 min. The resulting yellow solution was stirred at –78 °C for 1.5 h and then quenched with 5% AcOH in ethanol (20 mL). The cooling bath was removed, and the reaction mixture was allowed to warm up to rt. After being stirred at rt for 16 h the colourless solution was concentrated under vacuum. The residue was dissolved in Et_2O (20 mL), washed with sat. aq. $NaHCO_3$ (2 × 30 mL), brine (50 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column

chromatography (10% to 25% EtOAc in petroleum ether) to give the title products **266** and **267** (0.704 g, 53%) as a solid mixture of 2 diastereomers in a ratio 1:1. Crystals of **266** suitable for X-ray diffraction were grown by slow diffusion of hexane vapour into a solution of **266** in chloroform;

Title product **267**, a white solid; m.pt. 90–92 °C; R_f 0.57 (40% EtOAc-petroleum ether); δ_H (400 MHz, $CDCl_3$) 7.57 (1H, s, oxazole -CH=C*H*-), 7.04 (1H, s, oxazole -C*H*=CH-), 6.61 (1H, dd, *J* 18.0, 11.0 Hz, -C*H*=CH_2), 5.33 (1H, d, *J* 11.0 Hz, >C*H*-OH), 5.18 (1H, d, J_{cis} 12.5 Hz, -CH=CH_2), 5.14 (1H, d, J_{trans} 19.0 Hz, -CH=CH_2), 2.35 (1H, br s, >CH-O*H*), 2.27 (1H, qd, *J* 13.0, 3.5 Hz), 2.13-2.03 (2H, m), 1.86-1.80 (1H, m), 1.67-1.06 (10H, m). 0.99-0.82 (2H, m); δ_C (75 MHz, $CDCl_3$) 166.6 (oxazole 4°), 142.6 (-*C*H=CH_2), 138.1 (oxazole 3°), 126.6 (oxazole 3°), 112.3 (-CH=*C*H_2), 68.8 (>*C*H-OH), 49.5 (3°), 46.3 (2°), 45.1 (3°), 40.6 (4°), 38.1 (2°), 30.3 (2°), 28.8 (2°), 28.4 (2°), 22.4 (2°), 18.4 (2°); ν_{max} (film) 3239, 2917, 2849, 1567, 1460, 1238 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{23}NO_2 + H)^+$, 262.1807, found, 262.1788; $(C_{16}H_{23}NO_2 + Na)^+$, 284.1626, found, 284.1602.

Title product **266** as a white solid; R_f 0.50 (40% EtOAc-petroleum ether), m.pt. 98–100 °C; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, s, oxazole -C*H*=CH-), 7.01 (1H, s, oxazole -C*H*=CH-), 6.34 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*-CH_2), 5.16 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 5.08 (1H, d, *J* 7.5 Hz, >C*H*-OH), 5.04 (1H, dd, J_{trans} 17.5, 1.5 Hz, -CH=CH_2), 3.45 (1H, br s, >CH-O*H*), 2.37-2.31 (1H, m), 2.26-2.21 (1H, m), 2.05-1.99 (1H, m), 1.73-1.07 (11H, m), 0.91-0.85 (1H, m), 0.62 (1H, qd, *J* 13.0, 3.5 Hz); δ_C (100 MHz, $CDCl_3$) 166.6 (oxazole 4°), 142.5 (-*C*H=CH_2), 138.0 (oxazole 3°), 126.6 (oxazole 3°), 112.4 (-CH=*C*H_2), 64.6 (>*C*H-OH), 48.4 (3°), 45.7 (2°), 43.8 (3°), 40.2 (4°), 38.1 (2°), 28.5 (2°), 27.9 (2°), 25.6 (2°), 21.9 (2°), 17.9 (2°); ν_{max} (film) 3239, 2917, 2849, 1567, 1460, 1238, 1071, 916, cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{23}NO_2 + H)^+$, 262.1807, found, 262.1787; $(C_{16}H_{23}NO_2 + Na)^+$, 284.1626, found, 284.1602.

2-((1R*,4aS*,8aR*,9S*,11S*)-9-Methyldecahydro-1,4a-(methanooxymethano)naphthalen-11-yl)oxazole (269)

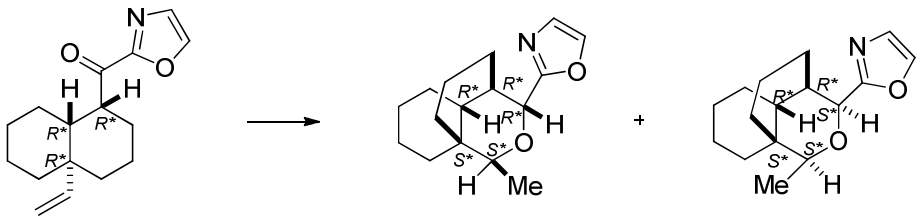


This was performed by adaptation of a literature procedure.[104] To a stirred TFA (10 mL) at rt was added sodium borohydride (468 mg, 12.4 mmol, 36.0 equiv) over a period of 10 min. To the viscous mixture, solution of **226** (90.0 mg, 0.344 mmol, 1.00 equiv) in DCM (10 mL) was added and the resulting mixture was refluxed for 3 h. Then reaction mixture was allowed to cool down to rt, carefully poured into 25% aq. NaOH/ice slurry (150 mL) to adjust the pH to 11, then extracted with Et_2O (2 × 25 mL). The organic extracts were combined, dried over $MgSO_4$ and then filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (30% EtOAc in petroleum ether) to give the product (60.4 mg, 67%) as an oily mixture of all four possible diastereomers. Only one of the four proved to be separable by column chromatography:

Title product **269**, R_f 0.36 (25% EtOAc-petroleum ether); δ_H (400 MHz, $CDCl_3$) 7.62 (1H, s, oxazole -C*H*=CH-), 7.09 (1H, s, oxazole -CH=C*H*-), 5.22 (1H, s,>C*H*-oxazole), 4.38 (1H, q, *J* 6.0 Hz, -O-C*H*(CH_3)-), 2.39-2.08 (3H, m), 2.04-1.92 (2H, m), 1.86-1.74 (1H, m, >C*H*-CH(Het)-O-), 1.65-1.24 (7H, m), 1.23 (3H, d, *J* 6.5 Hz, -O-CH(C*H*$_3$)-), 1.13-0.88 (3H, m); δ_C (75 MHz, $CDCl_3$) 164.0

(oxazole =*C*<), 138.3 (oxazole -*C*H=CH-), 126.8 (oxazole -CH=*C*H-), 72.9 (>*C*H-oxazole), 72.2 (-O-*C*H(CH_3)-), 45.4 (3°), 39.0 (3°), 36.8 (3°), 36.6 (2°) 34.5 (2°), 29.2 (4°), 26.7 (2°), 25.5 (2°), 21.8 (2°), 21.6 (2°), 15.0 (1°); ν_{max} (film) 2925, 2853, 1571, 1523, 1450, 1374, 1301, 1167, 1133, 1072, 1014, 913 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{23}NO_2 + H)^+$, 262.1807, found, 262.1817; $(C_{16}H_{23}NO_2 + Na)^+$, 284.1626, found, 284.1621.

2-((1R,4aS*,8aR*,9S*,11R*)-9-Methyldecahydro-1,4a-(methanooxymethano)naphthalen-11-yl)oxazole (270)*



275 **270** **269**

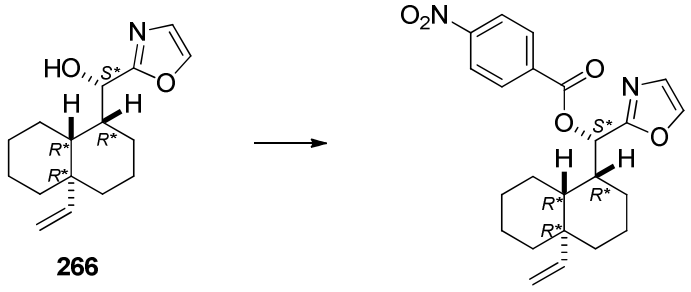
To a flask **275** (10.0 mg, 0.038 mmol, 1.00 equiv) was added zinc dust (50.4 mg, 0.771 mmol, 20.00 equiv) and a mixture of HCl (conc.) and water (3:1, 3 mL). The resulting mixture was refluxed for 30 min. Then reaction mixture was allowed to cool to rt andwas extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with sat. aq. $NaHCO_3$ (3 × 20 mL) dried over $MgSO_4$ and filtered. The filtrate was concentrated under vacuum to give the crude. Purification by column chromatography (25% EtOAc in petroleum ether) gave the product as two diastereomers:

The major diastereomer was the title product **270**, (5.6 mg, 56%), a colourless oil; R_f 0.29 (25% EtOAc-petroleum ether); δ_H (500 MHz, $CDCl_3$) 7.61 (1H, s, oxazole -C*H*=CH-), 7.11 (1H, s, -CH=C*H*-), 4.88 (1H, s,>C*H*-oxazole), 4.58 (1H, q, 6.0 Hz, -O-C*H*(CH_3)-), 2.36-1.26 (2H, m), 2.04-1.93 (2H, m), 2.04-1.93 (1H, m), 1.57-1.50 (4H, m), 1.45-1.41 (1H, m, >C*H*-CH(Het)-O-), 1.35-1.24 (2H, m), 1.22 (3H, d, *J* 6.5 Hz, -O-CH(C*H*$_3$)-), 1.19-0.78 (4H, m); δ_C (125 MHz, $CDCl_3$)

165.5 (oxazole =*C*<), 137.8 (oxazole -*C*H=CH-), 127.2 (oxazole -CH=*C*H-), 73.6 (-O-CH(*C*H_3)-), 68.8 (>CH-CH-*C*H(Het)-O-), 44.1 (>*C*H-CH-CH(Het)-O-), 37.7 (>CH-*C*H-CH(Het)-O-), 37.0 (2°), 36.5 (2°) 34.7 (4°), 34.3 (2°), 27.0 (2°), 25.9 (2°), 21.7 (2°), 21.4 (2°), 15.1 (1°); ν_{max} (film) 2922, 2854,1453, 1380, 1170, 1134, 1092, 911, 728 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{23}NO_2 + Na)^+$, 284.1626, found, 284.1647.

The minor diastereomer was compound **269**, (0.7 mg, 7%), a colourless oil; R_f 0.36 (25% EtOAc-petroleum ether). Spectroscopic data corresponds to that reported for compound **269**.

(S)-Oxazol-2-yl((1R*,4aR*,8aR*)-4a-vinyldecahydronaphthalen-1-yl)methyl 4-nitrobenzoate (274)*

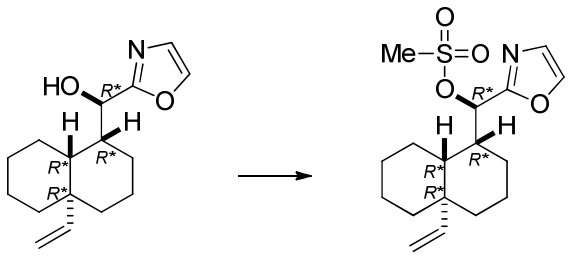


266 **274**

This was performed by adaptation of a literature procedure.[164] To a stirred solution of alcohol **266** (30.0 mg, 0.114 mmol, 1.00 equiv) in anhydrous DCM (5 mL), were added 4-nitrobenzoyl chloride (22.3 mg, 0.120 mmol, 1.05 equiv), pyridine (18.1 µL, 0.229 mmol, 2.00 equiv), and catalytic amounts of DMAP (1.3 mg, 10 mol%). The resulting reaction mixture was stirred at rt for 16 h. After completion of reaction, the reaction mixture was quenched by addition of aq. 0.5N NaOH (5 mL) and extracted with DCM (2 × 15 mL). The combined extracts were washed with water (2 × 15 mL) and brine (2 × 15 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude. Purified by column chromatography (25% EtOAc in petroleum ether) to give the title product **274**

(16.4 mg, 35%) as pale yellow solid, m.pt. 79–81 °C; R_f 0.62 (25% EtOAc in petroleum ether); δ_H (250 MHz, $CDCl_3$) 8.26 (2H, d, *J* 8.5 Hz, Ar-*H*), 8.19 (2H, d, *J* 8.5 Hz, Ar-*H*), 7.65 (1H, s, oxazole -C*H*-CH-), 7.14 (1H, s, oxazole -CH-C*H*-), 6.62 (1H, d, *J* 11.0 Hz, >C*H*-O-CO-), 6.44 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*-CH_2), 5.28 (1H, d, J_{cis} 11.0 Hz, -CH=CH_2), 5.14 (1H, d, J_{trans} 17.5 Hz, -CH=CH_2), 2.70-2.61 (1H, m, >C*H*-CH(Het)-), 2.13-0.61 (15H, m); δ_C (100 MHz, $CDCl_3$) 163.4 (>C=O), 162.1 (oxazole, 4°), 150.6 (Ar-*C*-NO_2), 141.8 (-*C*H=CH_2), 138.6 (oxazole -*C*H-CH-), 135.1 (Ar-*C*-CO_2-), 130.9 (Ar-*C*H), 127.7 (oxazole -CH-C*H*-), 123.5 (Ar-*C*H), 113.1 (-CH=*C*H_2), 68.2 (>*C*H(Het)-O-), 48.4 (3°), 45.8 (4°), 42.2 (3°), 40.2 (2°), 37.9 (2°), 29.0 (2°), 27.9 (2°), 25.6 (2°), 21.9 (2°), 18.0 (2°); ν_{max} (film) 2927, 2854, 1727, 1607, 1528, 1452, 1345, 1267, 1100, 1013, 913 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{23}H_{26}N_2O_5 + H)^+$, 411.1919, found, 411.1944; $(C_{23}H_{26}N_2O_5 + Na)^+$, 433.1739, found, 433.1768.

(R)-Oxazol-2-yl((1R*,4aR*,8aR*)-4a-Vinyldecahydronaphthalen-1-yl)methyl methanesulfonate (273)*

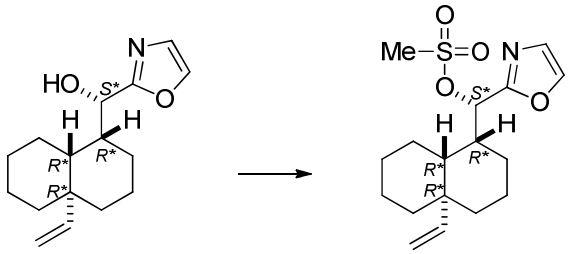


267 **273**

This was performed by adaptation of a literature procedure.[168] To a mixture of the alcohol **267** (5.9 mg, 0.025 mmol, 1.00 equiv) and DMAP (0.3 mg, 10 mol%) in anhydrous DCM (5 mL) was added methanesulfonyl chloride (2.2 µL, 0.028 mmol, 1.25 equiv) and Et_3N (12.6 µL, 0.090 mmol, 4.00 equiv) at 0 °C. The resulting mixture was allowed to warm up to rt stirred for 6 h under N_2 atmosphere. The reaction mixture then was diluted with DCM (10 mL), washed with water (2 × 5 mL), aq. $NaHCO_3$ (10 mL), brine (5 mL). The combined

organic layers were dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (25% EtOAc in petroleum ether) to give the title product **273** (1.0 mg, 18%) as a colourless oil, R_f 0.31 (25% EtOAc-petroleum ether); δ_H (250 MHz, $CDCl_3$) 7.68 (1H, s, oxazole -C*H*-CH-), 7.14 (1H, s, oxazole -CH-C*H*-), 6.65 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*=CH_2), 6.22 (1H, d, *J* 11.0 Hz, -C*H*(OMs)-Het), 5.31 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 5.17 (1H, dd, J_{trans} 18.0, 1.5 Hz, -CH=CH_2), 2.68 (3H, s, CH_3-SO_2-), 2.42-2.33 (1H, m), 2.27-1.99 (4H. m), 1.93-1.82 (2H, m), 1.74-1.04 (7H, m), 0.94-0.82 (2H, m); δ_C (75 MHz, $CDCl_3$) 161.0 (oxazole 4°), 141.5 (-*C*H=CH_2), 139.1 (oxazole -*C*H-CH-), 127.4 (oxazole -CH-*C*H-), 113.2 (-CH=*C*H_2), 76.3 (>*C*H(OMs)-Het), 48.8 (2°), 46.1 (2°), 42.9 (3°), 40.3 (4°), 38.6 (1°), 37.4 (3°), 29.9 (2°), 28.3 (2°), 27.7 (2°), 22.1 (2°), 18.1 (2°); ν_{max} (film) 3367, 2921, 2852, 1652, 1452, 1362, 1175, 1044, 916, 850, 778 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{17}H_{25}NO_4S + H)^+$, 340.1582, found, 340.1555; $(C_{17}H_{25}NO_4S + Na)^+$, 362.1401, found, 362.1371.

(S)-Oxazol-2-yl((1R*,4aR*,8aR*)-4a-vinyldecahydronaphthalen-1-yl)methyl methanesulfonate (271)*

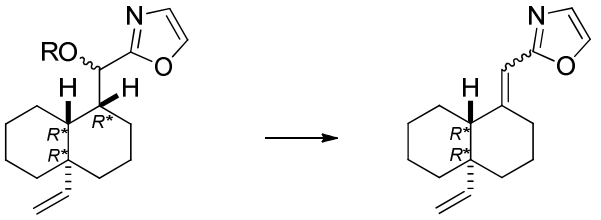


266 **271**

This was performed by adaptation of a literature procedure.[168] To a mixture of the alcohol **266** (10 mg, 0.038 mmol, 1.00 equiv) and DMAP (0.5 mg, 10 mol%) in anhydrous DCM (10 mL) was added methanesulfonyl chloride (3.7 µL, 0.047 mmol, 1.25 equiv) and Et_3N (21.0 µL, 0.152 mmol, 4.00 equiv) at 0 °C. The resulting mixture was allowed to warm up to rt stirred for 16 h. The reaction

mixture was diluted with DCM (15 mL), washed with water (2 × 15 mL), aq. $NaHCO_3$ (20 mL) and brine (20 mL). The combined organic layers were dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure to give the crude. Purification by column chromatography (25% EtOAc in petroleum ether) gave the title product **271** (12.1 mg, 93%) as a colourless oil: R_f 0.29 (25% EtOAc-petroleum ether); δ_H (500 MHz, $CDCl_3$) 7.71 (1H, s, oxazole -C*H*=CH-), 7.20 (1H, s, oxazole -CH=C*H*-), 6.33 (1H, dd, *J* 18.0, 11.0 Hz, -C*H*=CH_2), 6.12 (1H, d, *J* 12.0 Hz, -C*H*(OMs)-Het), 5.32 (1H, dd, J_{cis} 11.0, 0.5 Hz, -CH=CH_2), 5.19 (1H, dd, J_{trans} 18.0, 1.0 Hz, -CH=CH_2), 2.71 (3H, s, CH_3-SO_2-), 2.53-2.49 (1H, m), 2.33-2.22 (2H, m), 2.13-2.23 (2H, m), 1.86-1.07 (7H, m), 0.98-0.66 (2H, m), 0.43 (1H, qd, *J* 13.0, 4.0 Hz); δ_C (125 MHz, $CDCl_3$) 160.9 (oxazole 4°), 141.6 (-*C*H=CH_2), 139.7 (oxazole -*C*H=CH-), 127.9 (oxazole -CH=*C*H-), 113.5 (-CH=*C*H_2), 74.5 (>*C*H(OMs)-Het), 48.2 (3°), 45.7 (2°), 42.4 (2°), 40.2 (4°), 38.4 (1°), 37.8 (3°), 29.1 (2°), 27.9 (2°), 25.4 (2°), 21.8 (2°), 17.9 (2°); ν_{max} (film) 3408, 2921, 2852, 1634, 1452, 1362, 1175, 906 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{17}H_{25}NO_4S + H)^+$, 340.1582, found, 340.1555; $(C_{17}H_{25}NO_4S + Na)^+$, 362.1401, found, 362.1371.

2-(((4aR*,8aR*)-4a-Vinyldecahydronaphthalen-1-ylidene)methyl)oxazole (272)



R = H, **267**
Ms, **271** and **273**

272

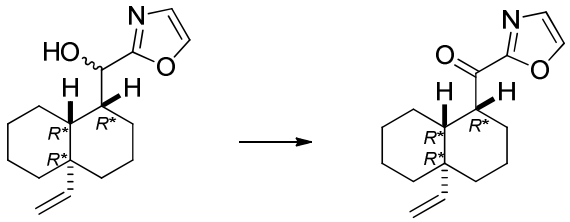
Procedure A

This was performed by adaptation of a literature procedure.[106] To a mixture of mesylates **271** and **273** (33.0 mg, 0.097 mmol, 1.00 equiv) in 1.2-dimethoxyethane (10 mL) sodium iodide (80.0 mg, 0.534 mmol, 5.50 equiv) and zinc dust (0.762 g, 11.7 mmol, 120 equiv) were added. The resulting mixture was heated in an oil bath at 120 °C for 16 h. The resulting mixture was cooled down to rt before dilution with water (15 mL) and filtration through a celite pad. The filtrate was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, then filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (5 to 15% EtOAc in petroleum ether) to give the title product **272** (15.0 mg, 64%) as a colourless oil, R_f 0.77 (25% EtOAc-petroleum ether); δ_H (250 MHz, $CDCl_3$) 7.57 (1H, s, oxazole -C*H*=CH-), 7.16 (1H, s, oxazole -CH=C*H*-), 5.96 (1H, br s >C=C*H*-Het), 5.82 (1H, dd, *J* 18.0, 11.0 Hz, -C*H*=CH_2), 5.12 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 5.02 (1H, dd, J_{trans} 18.0, 1.5 Hz, -CH=CH_2), 3.93-3.88 (1H, m), 2.37-2.28 (1H, m), 2.17-0.70 (13 H, m); δ_C (75 MHz, $CDCl_3$) 154.6 (oxazole 4°), 141.4 (-*C*H=CH_2), 137.9 (oxazole -*C*H=CH-), 130.9 (>C=*C*H-Het), 127.4 (oxazole -*C*H=CH-), 114.3 (-CH=*C*H_2), 107.6 (>*C*=CH-Het), 52.6 (4°), 44.4 (2°), 42.6 (2°), 40.0 (3°), 31.2 (2°), 26.6 (2°), 25.2 (2°), 23.4 (2°), 22.1 (2°); ν_{max} (film) 2925, 2852, 1650, 1451, 1363, 1103, 908 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{21}NO + H)^+$, 244.1701, found, 244.1713.

Procedure B

This was performed by adaptation of a literature procedure.[168] To a mixture of the alcohol **267** (5.9 mg, 0.025 mmol, 1.00 equiv) and DMAP (0.3 mg, 10 mol%) in anhydrous DCM (5 mL) was added methanesulfonyl chloride (2.2 µL 0.028 mmol, 1.25 equiv) and Et_3N (12.7 µL, 0.090 mmol, 4.00 equiv) at 0 °C. The resulting mixture was allowed to warm up to rt stirred for 6 h under N_2 atmosphere. The reaction mixture was diluted with DCM (10 mL), washed with water (2 × 5 mL), aq. $NaHCO_3$ (10 mL) and brine (5 mL). The combined organic layers were dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (25% EtOAc in petroleum ether) to give the title product **272** (4.4 mg, 81%) as a colourless oil. Spectroscopic data correspond to those reported in procedure A.

Oxazol-2-yl ((1R*,4aR*,8aR*)-4a-vinyldecahydronaphthalen-1-yl) ketone (275)

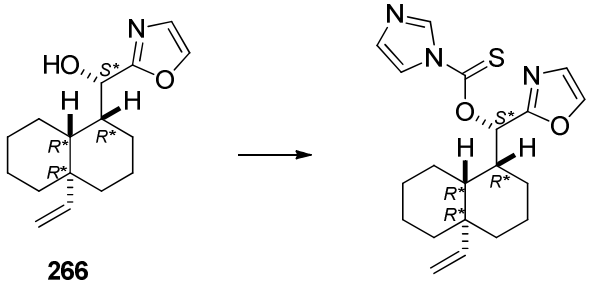


226 **275**

This was performed by adaptation of a literature procedure.[156] To a stirred solution of oxalyl chloride (53.3 mg, 36.0 µL, 0.420 mmol, 1.10 equiv) in DCM (10 mL) at –78 °C was added DMSO (64.2 mg, 58 µL, 0.820 mmol, 2.15 equiv). The solution was stirred for 25 min, and then alcohols **226** (100 mg, 0.38 mmol, 1.00 equiv) in dry DCM (5 mL) was added. The reaction mixture was stirred at –78 °C under nitrogen for 3 h, and then Et_3N (194 mg, 270 µL, 1.91 mmol, 5.00 equiv) was added at the same temperature. After 20 min the solution allowed to warm to rt over 30 min, then water (20 mL) was added and the reaction mixture

was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$, then filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (10 to 25% EtOAc in petroleum ether) to give the title compound **275** (85.0 mg, 86%) as a yellow colour oil; R_f 0.36 (20% EtOAc-petroleum ether); δ_H (250 MHz, $CDCl_3$) 7.77 (1H, s, oxazole -C*H*=CH-), 7.27 (1H, s, oxazole -CH=C*H*-), 6.23 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*=CH_2), 5.10 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 4.98 (1H, dd, J_{trans} 17.5, 1.5 Hz, -CH=CH_2), 3.83 (1H, t, *J* 6.0 Hz, >C*H*-CO-Het), 2.15-1.09 (15H, m); δ_C (62.5 MHz, $CDCl_3$) 192.5 (>CH-*C*O-Het), 159.0 (oxazole 4°), 141.7 (-*C*H=CH_2), 141.1 (oxazole -*C*H=CH-), 128.4 (oxazole -CH=*C*H-), 112.4 (-CH=*C*H_2), 48.0 (3°), 45.8 (3°), 44.0 (2°), 40.5 (4°), 40.0 (2°), 29.0 (2°), 27.6 (2°), 27.6 (2°), 21.8 (2°), 19.1 (2°); ν_{max} (film) 2925, 2850, 1692, 1482, 1449, 1353, 1247, 1150, 1105, 975, 923 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{21}NO_2 + H)^+$, 260.1650, found, 260.1679; $(C_{16}H_{21}NO_2 + Na)^+$, 282.1469, found, 282.1459.

O-((S)-Oxazol-2-yl((1R*,4aR*,8aR*)-4a-vinyldecahydronaphthalen-1-yl)methyl) 1H-imidazole-1-carbothioate (276)*

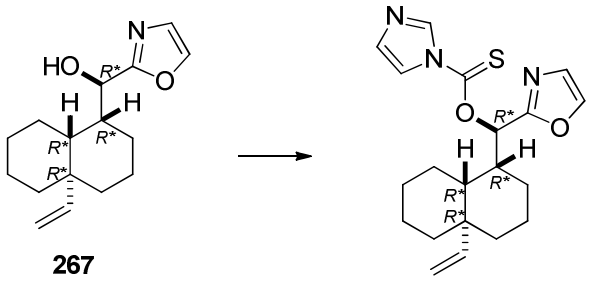


266 **276**

This was performed by adaptation of a literature procedure.[169] To a stirred solution of **266** (44.0 mg, 0.168 mmol, 1.00 equiv) in anhydrous DCM (10 mL) was added DMAP (2.5 mg, 10 mol%) followed by 1,1'-thiocarbonyldiimidazole (37.5 mg 0.210 mmol, 1.25 equiv). The reaction mixture was stirred for 16 h at

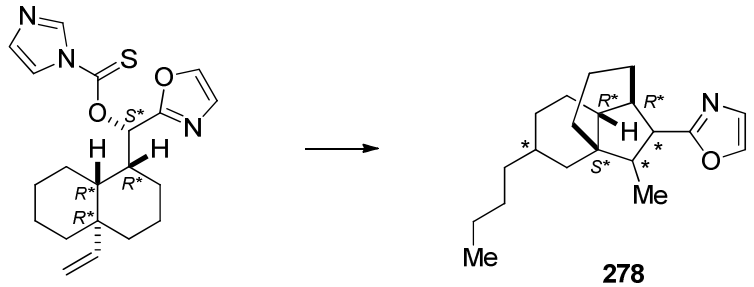
rt. Then solvent was removed under reduced pressure to give the crude. Purification by column chromatography (25 to 50% EtOAc in petroleum ether) gave the title product **276** (52.0 mg, 83%) as a pale yellow oil: R_f 0.24 (50% EtOAc-petroleum ether); δ_H (300 MHz, $CDCl_3$) 8.30 (1H, s, -C*H*=N-CH=CH-), 7.65 (1H, d, *J* 0.5 Hz, oxazole -C*H*=CH-), 7.60 (1H, s, -CH=N-CH=C*H*-), 7.15 (1H, d, *J* 0.5 Hz, oxazole -CH=C*H*-), 7.07 (1H, d, *J* 10.5 Hz, >CH-C*H*(OHet)-CS-), 6.99 (1H, s, -CH=N-C*H*=CH-), 6.40 (1H, ddd, *J* 17.5, 11.0, 1.0 Hz, -C*H*=CH_2), 5.30 (1H, dd, J_{cis} 11.0, 1.0 Hz, -CH=CH_2), 5.12 (1H, dd, J_{trans} 17.5, 1.5 Hz, -CH=CH_2), 2.75-2.67 (1H, m, >C*H*-CH(OHet)-CS-), 2.13-2.05 (1H, m), 2.00-1.92 (1H, m), 1.78-1.49 (4H, m), 1.47-1.08 (6H, m), 1.01-0.83 (2H, m), 0.65 (1H, qd, *J* 13.0, 3.5 Hz); δ_C (75 MHz, $CDCl_3$) 182.6 (-C(=S)-O), 160.6 (oxazole 4°), 141.2 (-*C*H=CH_2), 139.0 (oxazole -*C*H=CH-), 136.8 (-*C*H=N-CH=CH-N<), 130.8 (-CH=N-CH=*C*H-N<), 127.8 (oxazole -CH=*C*H-), 118.0 (imidazole -CH=N-*C*H=CH-N<), 113.2 (-CH=*C*H_2), 75.9 (>*C*H(OHet)-CS-), 48.5 (3°), 45.6 (2°), 42.4 (3°), 40.1 (4°), 37.7 (2°), 29.0 (2°), 27.9 (2°), 25.5 (2°), 21.8 (2°), 18.4 (2°); ν_{max} (film) 2924, 2852, 1463, 1386, 1312, 1283, 1219, 1102, 968, 914, 855, 764 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{20}H_{25}N_3O_2S + H)^+$, 372.1745, found, 372.1755; $(C_{20}H_{25}N_3O_2S + Na)^+$, 394.1565, found, 394.1604.

O-((R*)-Oxazol-2-yl((1R*,4aR*,8aR*)-4a-vinyldecahydronaphthalen-1-yl)methyl) 1H-imidazole-1-carbothioate (277)



This was performed by adaptation of a literature procedure.[169] To a stirred solution of **267** (85.0 mg, 0.325 mmol, 1.00 equiv) in anhydrous DCM (10 mL) was added DMAP (4.0 mg, 10 mol%) followed by 1,1'-thiocarbonyldiimidazole (72.4 mg 0.406 mmol, 1.25 equiv). The corresponding reaction solution was stirred for 16 h at rt. Then solvent was removed under reduced pressure to give the crude. Purification by column chromatography (25 to 45% EtOAc in petroleum ether) gave the title product **277** (61.0 mg, 51%) as a pale yellow oil: R_f 0.10 (40% EtOAc-petroleum ether); δ_H (250 MHz, $CDCl_3$) 8.37 (1H, s, -C*H*=N-CH=CH-), 7.66 (1H, s, -CH=N-CH=C*H*-), 7.59 (1H, s, oxazole -C*H*=CH-), 7.08 (1H, s, oxazole -CH=C*H*-), 7.03 (1H, s, -CH=N-C*H*=CH-), 6.92 (1H, d, *J* 11.0 Hz, >CH-C*H*(OHet)-CS-), 6.31 (1H, dd, *J* 17.5, 11.0 Hz, -C*H*=CH_2), 5.25 (1H, dd, J_{cis} 11.5, 1.0 Hz, -CH=CH_2), 5.18 (1H, dd, J_{trans} 17.5, 1.0 Hz, -CH=CH_2), 2.60-2.52 (1H, m, >C*H*-CH(OHet)-CS-), 2.15-2.07 (1H, m), 1.83-0.83 (14H, m); δ_C (75 MHz, $CDCl_3$) 182.1 (-C(=S)-O), 160.9 (oxazole 4°), 141.4 (-*C*H=CH_2), 138.9 (-*C*H=N-CH=CH-N<), 138.7 (oxazole -*C*H=CH-), 130.9 (-CH=N-CH=*C*H-N<), 127.4 (oxazole -CH=*C*H-), 118.2 (imidazole -CH=N-*C*H=CH-N<), 113.5 (-CH=*C*H_2), 78.8 (>*C*H(OHet)-CS-), 48.6 (3°), 45.8 (2°), 42.4 (3°), 40.1 (4°), 37.3 (2°), 29.7 (2°), 28.3 (2°), 28.1 (2°), 21.9 (2°), 18.1 (2°); ν_{max} (film) 2930, 2847, 1466, 1361, 1315, 1258, 1221, 1107, 971, 909 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{20}H_{25}N_3O_2S + H)^+$, 372.1745, found, 372.1755; $(C_{20}H_{25}N_3O_2S + Na)^+$, 394.1565, found, 394.1604.

2-((1R*,4aS*,8aR*)-6-Butyl-9-methyldecahydro-1,4a-ethanonaphthalen-10-yl)oxazole (278)



276 **278**

Procedure A

This was performed by adaptation of a literature procedure.[115] To a stirred solution of **276** (50.0 mg, 0.130 mmol, 1.00 equiv) in anhydrous benzene (10 mL), was added *n*-Bu_3SnH (79.8 mg, 73.7 µL, 0.270 mmol, 2.00 equiv) and the resulting mixture was heated under reflux for 30 min. After consumption of **276** by monitoring on TLC, the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (10 to 20% EtOAc in petroleum ether) to give the title compound **278** (19.0 mg, 45%) as a single isomer and a colourless oil; R_f 0.26 (10% EtOAc in petroleum ether); δ_H (500 MHz, $CDCl_3$) 7.54 (1H, s, oxazole -CH=CH-), 7.01 (1H, s, oxazole -CH=CH-), 2.81 (1H, pent, *J* 7.5 Hz), 2.74 (1H, d, *J* 7.5 Hz), 2.33 (1H, d, *J* 3.0 Hz), 1.71-1.55 (8H, m), 1.48-1.24 (11H, m), 1.19-1.02 (3H, m), 1.07 (3H, d, *J* 7.0 Hz), 0.91 (3H, t, *J* 7.0 Hz) ; δ_C (125 MHz, $CDCl_3$) 169.3 (oxazole 4°), 137.8 (oxazole -*C*H=CH-), 126.5 (oxazole -CH=*C*H-), 53.3 (3°), 47.7 (3°), 44.7 (3°), 44.4 (4°), 38.2 (3°), 37.0 (2°), 33.1 (2°), 32.0 (2°), 27.8 (2°), 26.8 (2°), 26.4 (2°), 25.9 (2°), 21.4 (2°), 19.8 (2°), 17.4 (2°), 13.5 (1°), 11.4 (1°); ν_{max} (film) 2922, 2856, 1563, 1451, 1377, 1133, 1101, 1075, 915, 740 cm^{-1}; TOF-ESI+ m/z calculated for $(C_{20}H_{31}NO + H)^+$, 302.2478, found, 302.2413.

Procedure B

To a stirred solution of **276** (55.0 mg, 0.140 mmol, 1.00 equiv) in anhydrous toluene (5 mL), was added *n*-Bu_3SnH (108 mg, 100 µL, 0.37 mmol, 2.50 equiv) and AIBN (2.4 mg, 0.01 mol, 10mol%), and the resulting mixture was heated under reflux for 1 h. After consumption of starting material by monitoring on TLC, the mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (5 to 40% EtOAc in petroleum ether) to give the the title compound **278** (26.0 mg, 56%) a colourless oil. Spectroscopic data correspond to those reported in procedure A.

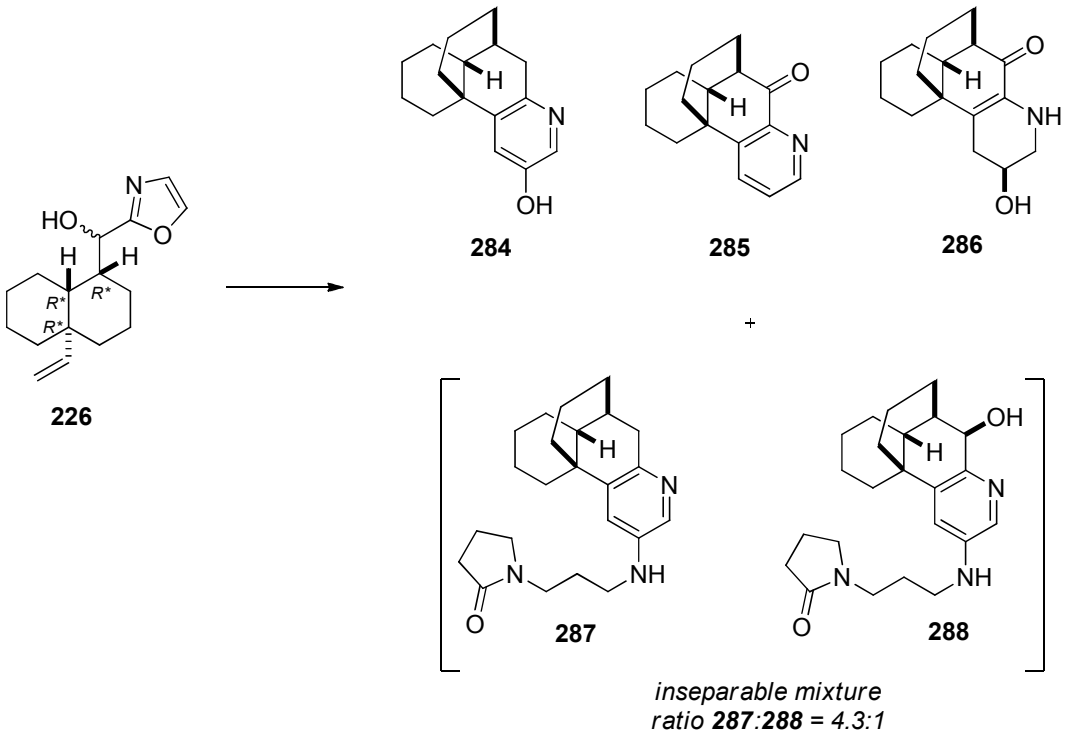
(6S*,6aR*,10aS*)-6,6a,7,8,9,10-Hexahydro-5H-6,10a-propanobenzo[f]quinolin-2-ol (284)

(6R*,6aR*,10aS*)-6,6a,7,8,9,10-Hexahydro-5H-6,10a-propanobenzo[f]quinolin-5-one (285)

(6R*,6aR*,10aS*)-2-Hydroxy-3,4,6,6a,7,8,9,10-octahydro-1H-6,10a-propanobenzo[f]quinolin-5(2H)-one (286)

(6R*,6aR*,10aS*)-5-(Hexahydropyrrolo[1,2-a]pyrimidin-1(2H)-yl)-6,6a,7,8,9,10-hexahydro-5H-6,10a-propanobenzo[f]quinolin-2-ol (287)

1-(3-(((5R*,6R*,6aR*,10aS*)-5-hydroxy-6,6a,7,8,9,10-hexahydro-5H-6,10a-propanobenzo[f]quinolin-2-yl)amino)propyl)pyrrolidin-2-one (288)



To a microwave vial charged with a stirring bar, substrate **226** (260 mg, 0.994 mmol, 1.00 equiv), anhydrous toluene (10 mL) and DBN (2.47 g, 2.45 mL, 19.9

mmol, 20.0 equiv) were added. The reaction mixture was degassed with argon and irradiated in microwave reactor at 200 °C for 90 min. After completion of reaction, the reaction solvent was removed under reduced pressure. The brown residue was diluted with EtOAc (20 mL) washed with water (2 × 15 mL) and brine (30 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (elution gradient 0:0:80:20 to 5:10:100:0 (Et_3N:MeOH:EtOAc:petrol)) to give the title products:

Title product **284** (13 mg, 5%) as pale yellow oil; R_f 0.25 (100% EtOAc); δ_H (500 MHz, $CDCl_3$) 8.18 (1H, d, *J* 1.5 Hz, pyridine -N=C*H*-C(OH)=CH-), 7.22 (1H, d, *J* 1.5 Hz, pyridine -N=C*H*-C(OH)=CH-), 3.14 (1H, dd, *J* 18.0, 7.0 Hz, Py-CH_2-CH<), 2.72 (1H, d, *J* 18.0 Hz, Py-CH_2-CH<), 2.20 (1H, d, *J* 14.0 Hz, Py-4°C-C*H*H-), 2.02-1.96 (2H, m, Py-CH_2-C*H*< & one other alkyl H), 1.78-1.72 (2H, m), 1.68-0.85 (13 H, m); δ_C (125 MHz, $CDCl_3$) 153.4 (pyridine -N=CH-*C*(OH)=CH-), 148.9 (pyridine 4°), 138.8 (pyridine 4°), 132.5 (pyridine -N=*C*H-C(OH)=CH-), 122.7 (pyridine -N=CH-C(OH)=*C*H-), 44.4 (3°), 42.8 (3°), 39.3 (2°), 36.8 (2°), 35.0 (2°), 33.3 (4°), 32.5 (2°), 28.2 (2°), 26.7 (2°), 22.1 (2°), 18.9 (2°); ν_{max} (film) 3423, 2936, 2885, 2831, 1527, 1453, 1343, 1301, 1268, 1204, 1123, 1019, 985, 907 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{21}NO + Na)^+$, 266.1516, found, 266.1515.

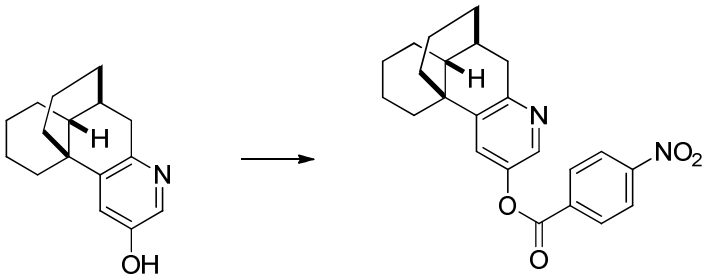
Title product **285** (4 mg, 2%) as pale yellow oil; R_f 0.28 (100% EtOAc); δ_H (500 MHz, $CDCl_3$) 8.69 (1H, d, *J* 4.0 Hz, pyridine -N=C*H*-CH=CH-) 7.73 (1H, d, *J* 8.0 Hz, pyridine -N=CH-CH=C*H*-), 7.48 (1H, dd, *J* 8.0, 4.5 Hz, pyridine -N=CH-C*H*=CH-), 2.36 (1H, d, *J* 14.0 Hz), 2.17 (1H, app s), 1.89-1.78 (2H, m), 1.69-0.83 (12 H, m); δ_C (125 MHz, $CDCl_3$) 200.6 (>C=O), 150.2 (pyridine 4°), 148.1 (pyridine -N=*C*H-CH=CH-), 142.7 (pyridine 4°), 135.3 (pyridine -N=CH-CH=*C*H-), 127.9 (pyridine -N=CH-*C*H=CH-), 50.1 (3°), 47.4 (3°), 40.4 (2°), 40.1 (4°), 36.7 (2°), 30.3 (2°), 29.6 (2°), 26.4 (2°), 21.6 (2°), 18.9 (2°); ν_{max} (film) 2933, 2881, 1701, 1542, 1473, 1389, 1325, 1277, 1215, 1157, 998, 911 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{19}NO + H)^+$, 242.1544, found, 242.1539.

Title product **286** (30 mg, 12%) colourless oil; R_f 0.40 (100% EtOAc); δ_H (500 MHz, $CDCl_3$) 4.26 (1H, br s, -CH_2-CH(O*H*)-CH_2-), 4.20-4.14 (1H, m, -CH_2-C*H*(OH)-CH_2-NH-) 3.20 (1H, dt, *J* 11.0, 3.0 Hz, -CH_2-CH(OH)-C*H*$_2$-NH-) 2.98 (1H, dt, *J* 11.0, 1.5 Hz, -CH_2-CH(OH)-C*H*$_2$-NH-), 2.57 (1H, br s, -CH_2-N*H*-), 2.37 (1H, ddd, *J* 19.0, 4.0, 1.5 Hz, -C*H*$_2$-CH(OH)-CH_2-NH-), 2.31-2.27 (1H, m), 1.98 (1H, dq, *J* 19.5, 2.0 Hz, -C*H*$_2$-CH(OH)-CH_2-NH-), 1.86-1.77 (2H, m), 1.73-0.83 (13H, m); δ_C 62.5 MHz, $CDCl_3$) 196.4 (>C=O), 138.4 (>*C*=C<), 124.4 (>C=*C*<), 62.7 (>*C*(OH)<), 48.5 (>C(OH)-*C*H_2-NH-), 48.1 (3°), 45.9 (3°), 39.6 (4°), 35.7 (2°), 35.0 (2°), 31.6 (2°), 28.3 (2°), 27.8 (2°), 26.0 (2°), 23.1 (2°), 19.1 (2°); ν_{max} (film) 3357, 3251, 2947, 2851, 1705, 1552, 1414, 1369, 1284, 1105, 1078, 999, 911, 871 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{23}NO_2 + Na)^+$, 284.1626, found, 284.1642.

Title product **287** (41.9 mg, 11%) colourless oil; R_f 0.17 (1:5:100 (Et_3N:MeOH:EtOAc)); δ_H (500 MHz, $CDCl_3$) 7.79 (1H, d, *J* 2.5 Hz, pyridine -N=C*H*-C(OH)=CH-) 6.75 (1H, d, *J* 2.5 Hz, pyridine -N=CH-C(OH)=C*H*-), 4.18 (1H, br s, -N*H*-), 3.37-3.33 (4H, m, Py-NH-CH_2-CH_2-C*H*$_2$- and -C(O)N-C*H*$_2$-CH_2-CH_2-), 3.14-3.08 (2H, m, Py-NH-C*H*$_2$-CH_2-CH_2-), 3.04 (1H, dd, *J* 18.0, 7.0 Hz, Py-C*H*$_2$-CH<), 2.58 (1H, d, *J* 18.0 Hz, Py-C*H*$_2$-CH<), 2.37 (2H, t, *J* 8.0 Hz, -CH_2-C*H*$_2$-C(O)N-CH_2-), 2.17-2.14 (1H, m, Py-C(4°)-C*H*$_2$-), 2.02-1.96 (2H, m, -C(O)N-CH_2-C*H*$_2$-CH_2-), 1.93-1.91 (1 H, m, Py-CH_2-C*H*<), 1.79-1.74 (2H, m, Py-NH-CH_2-C*H*$_2$-CH_2-), 1.73-0.99 (14H, m); δ_C (125 MHz, $CDCl_3$) 175.3 (-*C*(O)N<), 147.5 (pyridine 4°), 142.3 (pyridine -N=CH-*C*(NH-)=CH-), 136.4 (pyridine 4°), 132.0 (pyridine -N=*C*H-C(NH-)=CH-), 117.4 (pyridine -N=CH-C(NH-)=*C*H-), 47.1 (-C(O)N-*C*H_2-) 44.7 (2°), 42.9 (3°), 40.4 (-NH-*C*H_2-CH_2-CH_2-), 39.7 (-NH-CH_2-CH_2-*C*H_2-), 39.0 (4°), 36.8 (2°), 35.1 (2°), 34.3 (Py-*C*H_2-CH<), 32.8 (Py-CH_2-*C*H<), 30.8 (-CH_2-*C*H_2-C(O)N-CH_2-), 28.2 (2°), 26.8 (2°), 25.8 (-NH-CH_2-*C*H_2-*C*H_2-), 22.1 (2°), 19.0 (2°), 17.8 (-*C*H_2-CH_2-C(O)N-CH_2-); ν_{max} (film) 3321, 2981, 2925, 2854, 1667, 1594, 1494, 1460, 1398, 1350, 1288, 1243, 1164, 1076, 1031, 953, 745, 662 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{23}H_{33}N_3O + H)^+$, 368.2796, found, 368.2859.

Title product **288** (12.6 mg, 3%) colourless oil; R_f 0.17 (1:5:100:0 (Et_3N:MeOH:EtOAc:petrol)); δ_H (500 MHz, $CDCl_3$) 7.82 (1H, d, *J* 2.5 Hz, pyridine -N=C*H*-C(OH)=CH-) 6.70 (1H, d, *J* 2.5 Hz, pyridine -N=CH-C(OH)=C*H*-), 4.72 (1H, d, *J* 7.0 Hz, Py-CH(O*H*)-CH<), 4.40 (1H, br s, -N*H*-), 3.37-0.99 (29H, m); δ_C (125 MHz, $CDCl_3$) 175.4 (-*C*ONH-), 148.5 (pyridine 4°), 143.5 (pyridine -N=CH-*C*(NH-)=CH-), 135.9 (pyridine 4°), 131.9 (pyridine -N=*C*H-C(NH-)=CH-), 116.4 (pyridine -N=CH-C(NH-)=*C*H-), 68.5 (Py-*C*H(OH)-CH<), 46.4, 43.4, 40.1, 39.7, 39.6, 37.3, 36.8, 29.6, 29.5, 29.2, 28.1, 27.0, 26.9, 25.7, 22.3, 18.9; ν_{max} (film) 3670, 3321, 2981, 2925, 2854, 1667, 1594, 1494, 1460, 1398, 1350, 1288, 1243, 1164, 1076, 1031, 953 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{23}H_{33}N_3O_2 + H)^+$, 384.2646, found, 384.2706.

(6S*,6aR*,10aS*)-6,6a,7,8,9,10-Hexahydro-5H-6,10a-propanobenzo[f]quinolin-2-yl 4-nitrobenzoate (289)

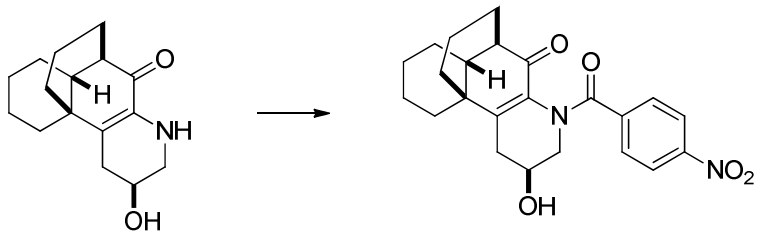


284 **289**

This was performed by adaptation of a literature procedure.[164] To a stirred solution of alcohol **284** (17 mg, 0.069 mmol, 1.00 equiv) in anhydrous DCM (3 mL), were added 4-nitrobenzoyl chloride (25.9 mg, 0.139 mmol, 2.00 equiv) and pyridine (27.6 mg, 28 µL, 0.349 mmol, 5.00 equiv). The reaction mixture was stirred at rt for 16 h. After completion of reaction, the reaction mixture was quenched by addition of aq. NaOH (1.0 M, 5 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were washed with water (15 mL) and brine (30 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (40 to 75%

EtOAc in petroleum ether) to give the title ester **289** (14 mg, 52%) as pale yellow solid, m.pt. 83–85 °C; R_f 0.47 (40% EtOAc in petroleum ether); δ_H (500 MHz, $CDCl_3$) 8.38 (2H, d, *J* 9.0 Hz, Ar-*H*), 8.36 (2H, d, *J* 9.0 Hz, Ar-*H*), 8.33 (1H, d, *J* 2.0 Hz, pyridine -N=C*H*-C(OH)=CH-), 7.43 (1H, d, *J* 2.0 Hz, pyridine -N=C*H*-C(OH)=CH-), 3.19 (1H, dd, *J* 18.5, 7.0 Hz, Py-CH_2-CH<), 2.77 (1H, d, *J* 18.5 Hz, Py-CH_2-CH<), 2.21-2.16 (1H, m), 2.07-2.03 (1H, m), 1.83-1.77 (1H, m), 1.73-1.65 (2H, m), 1.63-1.58 (1H, m, Py-CH_2-C*H*<), 1.56-1.50 (1H, m), 1.48-1.03 (9H, m); δ_C (125 MHz, $CDCl_3$) 163.1 (>C=O), 157.2 (pyridine 4°), 151.0 (Ar-*C*-NO_2), 145.7 (pyridine -N=CH-*C*(OPNB)=CH-), 139.1 (pyridine -N=*C*H-C(OPNB)=CH-), 137.8 (pyridine 4°), 134.5 (Ar-*C*-CO_2-), 131.3 (Ar-*C*H-), 126.2 (pyridine -N=CH-C(OPNB)=*C*H-), 123.7 (Ar-*C*H-), 44.3 (3°), 42.9 (2°), 39.5 (4°), 36.8 (2°), 35.1 (2°), 34.9 (2°), 32.6 (3°), 28.2 (2°), 26.7 (2°), 22.4 (2°), 18.9 (2°); ν_{max} (film) 2926, 2855, 1742, 1608, 1528, 1448, 1348, 1258, 1210, 1107, 1014, 907 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{23}H_{24}N_2O_4 + Na)^+$, 415.1633, found, 415.1633.

(6R*,10aS*)-5-Oxo-2,3,4,5,6,6a,7,8,9,10-decahydro-1H-6,10a-propanobenzo[f]quinolin-2-yl 4-nitrobenzoate (290)

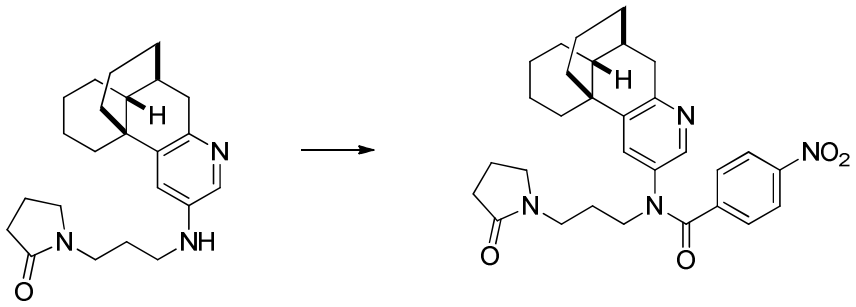


286 **290**

This was performed by adaptation of a literature procedure.[164] To a solution of **286** (30.0 mg, 0.114 mmol, 1.00 equiv) in anhydrous DCM (5 mL), were added 4-nitrobenzoyl chloride (42.5 mg, 0.229 mmol, 1.00 equiv), pyridine (45.3 mg, 46.3 µL, 0.573 mmol, 5.00 equiv), and catalytic amounts of DMAP (1.4 mg, 10 mol%). Resulting reaction mixture was stirred at rt for 16 h. After completion of

reaction, the reaction mixture was quenched by addition of aq. NaOH (1.00 M, 10 mL) and extracted with DCM (3 × 15 mL). The combined extracts were washed with water (15 mL) and brine (50 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (40 to 75% EtOAc in petroleum ether) to give the title ester **290** (63.6 mg, 83%) as pale yellow solid, m.pt. 92–94 °C; R_f 0.26 (75% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 8.14 (2H, d, *J* 6.0 Hz, Ar-*H*), 7.71 (2H, d, *J* 6.0 Hz, Ar-*H*), 4.46-4.31 (1H, m, >C*H*-OH), 3.16 (1H, br s, >CH-O*H*) , 2.67 (1H, dd, *J* 19.0, 5.0 Hz, -CH_2-CH(OH)-C*H*$_2$-N<), 2.22 (1H, d, *J* 19.0 Hz, -CH_2-CH(OH)-C*H*$_2$-N<), 2.15-2.09 (1H, m, -C*H*$_2$-CH(OH)-CH_2-), 1.97-1.94 (1H, m, -C*H*$_2$-CH(OH)-CH_2-), 1.78-1.44 (9H, m), 1.37-0.82 (7H, m); δ_C (75 MHz, $CDCl_3$) 192.7 (>C=O), 166.2 (-*C*(O)NPNB), 151.1 (Ar-*C*(4°)-NO_2), 137.1 (>*C*=C<), 134.7 (Ar-*C*(4°)-C(O)N<), 129.8 (Ar-*C*H-), 123.5 (>C=*C*<), 122.7 (Ar-*C*H), 65.9 (-CH_2-*C*H(OH)-CH_2-), 49.2 (-CH(OH)-*C*H_2-N<), 48.8 (3°), 46.7 (3°), 45.4 (2°), 40.0 (2°), 39.7 (4°), 38.1 (-*C*H_2-CH(OH)-CH_2-N<), 33.8 (2°), 29.6 (2°), 26.6 (2°), 22.1 (2°), 17.3 (2°); ν_{max} (film) 3433, 2925, 2854, 1673, 1635, 1523, 1345, 1066, 904, 723 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{23}H_{26}N_2O_5 + H)^+$, 411.1919, found, 411.1937; $(C_{23}H_{26}N_2O_5 + Na)^+$, 433.1739, found, 433.1737.

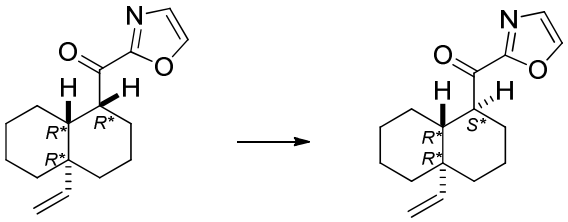
(6R*,6aR*,10aS*)-5-(Hexahydropyrrolo[1,2-a]pyrimidin-1(2H)-yl)-6,6a,7,8,9,10-hexahydro-5H-6,10a-propanobenzo[f]quinolin-2-yl 4-nitrobenzoate (291)



This was performed by adaptation of a literature procedure.[164] To a stirred solution of alcohol **287** (54.5 mg, 0.148 mmol, 1.00 equiv) in anhydrous DCM (5 mL), were added 4-nitrobenzoyl chloride (30.2 mg, 0.163 mmol, 1.10 equiv) and pyridine (23.4 mg, 24 µL, 0.296 mmol, 2.00 equiv. Resulting reaction mixture was stirred at rt for 14 h. After completion of reaction, the reaction mixture was quenched by addition of aq. NaOH (1.0 M, 5 mL) and extracted with DCM (3 × 10 mL). The combined extracts were washed with water (25 mL) and brine (40 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (40 to 85% EtOAc in petroleum ether) to give the title ester **291** (63.6 mg, 83%) as yellow oil; R_f 0.18 (75% EtOAc in petroleum ether); δ_H (300 MHz, $CDCl_3$) 8.14 (1H, d, *J* 2.0 Hz, pyridine -N=C*H*-C(OH)=CH-), 7.87 (2H, d, *J* 8.5 Hz, Ar-*H*), 7.35 (2H, d, *J* 8.5 Hz, Ar-*H*), 7.08 (1H, app s, pyridine -N=C*H*-C(OH)=CH-), 4.06-3.83 (2H, m), 3.43-3.31 (4H, m, Py-NPNB-CH_2-CH_2-CH_2- and -CH_2-C(O)N-CH_2-CH_2-), 3.15-3.05 (1H, m, -NPNB-CH_2-CH_2-CH_2-), 3.01 (1H, d, *J* 18.0, 7.0 Hz, Py-CH_2-CH<), 2.59 (1H, d, *J* 19.0 Hz, Py-CH_2-CH<), 2.36 (2H, t, *J* 8.0 Hz, -CH_2-C(O)N-CH_2-CH_2-), 2.07-1.82 (5H, m), 1.68-0.45 (14H, m); δ_C (75 MHz, $CDCl_3$) 175.1 (-CH_2-*C*(O)N<), 168.3 (-*C*(O)NPNB), 158.8 (Ar-*C*-NO_2), 147.8 (pyridine 4°), 144.2 (pyridine -N=CH-*C*(NPNB)=CH-), 141.9 (pyridine 4°), 137.7 (pyridine -N=*C*H-C(NPNB)=CH-), 136.3 (Ar-*C*-CO_2-), 133.3 (pyridine -N=CH-C(NPNB)=*C*H-),

129.3 (Ar-*C*H-), 123.0 (Ar-*C*H-), 46.9 (2°), 46.7 (2°) 43.8 (3°), 42.8 (2°), 39.3 (2°), 39.0 (4°), 36.2 (2°), 35.0 (2°), 34.5 (2°), 32.2 (3°), 30.8 (2°), 28.0 (2°), 26.4 (2°), 25.2 (2°), 21.8 (2°), 18.5 (2°), 17.8 (2°); ν_{max} (film) 2924, 2854, 1675, 1653, 1601, 1523, 1455, 1346, 1313, 1292, 1107, 863, 851, 753 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{30}H_{36}N_4O_4 + H)^+$, 517.2809, found, 517.2805.

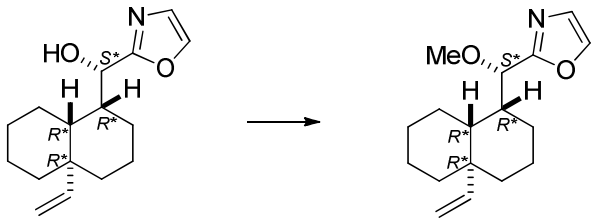
Oxazol-2-yl ((1S*,4aR*,8aR*)-4a-vinyldecahydronaphthalen-1-yl) ketone (296)



275 **296**

This was performed by adaptation of a literature procedure.[120] A mixture of ketone **275** (47.0 mg, 0.180 mmol, 1.00 equiv), DBN, (0.440 mL, 3.62 mmol, 2.00 equiv), and *o*-xylene (20 mL) was heated to reflux for 16 h. The reaction mixture then was concentrated under reduced pressure to give a brown oil, which was purified by column chromatography (25 to 30% EtOAc in petroleum ether) to give the title product **296** (27.7 mg, 59%) as a colourless oil; R_f 0.26 (30% EtOAc-petroleum ether); δ_H (250 MHz, $CDCl_3$) 7.81 (1H, s, oxazole -C*H*=CH-), 7.32 (1H, s, oxazole -CH=C*H*-), 6.20 (1H, dd, *J* 18.0, 11.0 Hz, -C*H*=CH_2), 5.21 (1H, d, J_{cis} 11.0 Hz, -CH=CH_2), 5.10 (1H, dd, J_{trans} 18.0, 1.5 Hz, -CH=CH_2), 3.66 (1H, dt, *J* 11.0, 3.0 Hz, >C*H*-CO-Het), 1.93-1.17 (15H, m); δ_C (62.5 MHz, $CDCl_3$) 192.7 (>CH-*C*O-Het), 158.3 (oxazole 4°), 141.7 (-*C*H=CH_2), 141.7 (oxazole -*C*H=CH-), 129.0 (oxazole -CH=*C*H-), 114.6 (-CH=*C*H_2), 47.3 (3°), 46.9 (3°), 41.4 (2°), 40.3 (4°), 40.3 (2°), 30.7 (2°), 26.5 (2°), 25.8 (2°), 21.8 (2°), 21.1 (2°); ν_{max} (film) 2925, 2857, 1694, 1537, 1481, 1448, 1387, 1269, 1210, 1135, 981, 904 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{16}H_{21}NO_2 + Na)^+$, 282.1469, found, 282.1476.

2-((S*)-Methoxy((1R*,4aR*,8aR*)-4a-Vinyldecahydronaphthalen-1-yl)methyl)oxazole (312)



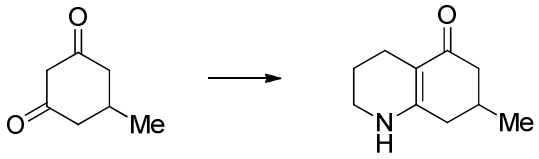
266 **312**

This was performed by adaptation of a literature procedure.[124] To a suspension of NaH (60% in mineral oil, 2.6 mg, 0.066 mmol, 1.25 equiv) in THF (3 mL), a solution of alcohol **266** (14.0 mg, 0.053 mmol, 1.00 equiv) in THF (2 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 20 min, and then MeI (10.2 µL, 0.066 mmol, 1.25 equiv) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 14 h. The reaction mixture was quenched by addition of water and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated Under reduced pressure, then purified by column chromatography (10% EtOAc in petrol) to give the title product **312** (12.0 mg, 81%) as pale yellow oil: R_f 0.23 (10% EtOAc-petroleum ether); δ_H (300 MHz, $CDCl_3$) 7.64 (1H, s, oxazole -C*H*=CH-), 7.12 (1H, d, *J* 0.5 Hz, oxazole -CH=C*H*-), 6.41 (1H, dd, *J* 18.0, 11.0 Hz, -C*H*=CH_2), 5.23 (1H, dd, J_{cis} 11.0, 1.5 Hz, -CH=CH_2), 5.09 (1H, dd, J_{trans} 18.0, 1.5 Hz, -CH=CH_2), 4.64 (1H, d, *J* 11.0 Hz, -C*H*(OCH_3)-Het), 3.15 (3H, s, -CH(OCH_3)-), 2.38-2.24 (2H, m), 2.08-2.00 (1H, m), 1.84-0.98 (11H, m), 0.90-0.71 (2H, m), 0.65-0.51 (1H, m); δ_C (75 MHz, $CDCl_3$) 164.2 (oxazole 4°), 143.0 (-*C*H=CH_2), 138.6 (oxazole -*C*H=CH-), 127.0 (oxazole -CH=*C*H-), 112.2 (-CH=*C*H_2), 74.1 (>*C*H(OCH_3)-Het), 56.8 (>CH(O*C*H_3)-Het), 48.4 (3°), 46.0 (2°), 43.1 (3°), 40.5 (4°), 38.5 (2°), 28.8 (2°), 28.0 (2°), 25.5 (2°), 22.0 (2°), 17.9 (2°); ν_{max} (film) 2924, 2853, 1566, 1450, 1235, 1133, 1083, 1039, 912, 850, 795, 739 cm^{-1}; TOF-ESI+ *m/z* calculated for

$(C_{17}H_{25}NO_2 + H)^+$, 276.1963, found, 276.1964; $(C_{17}H_{25}NO_2 + Na)^+$, 298.1782, found, 298.1800.

4.3 Synthetic procedures for real system

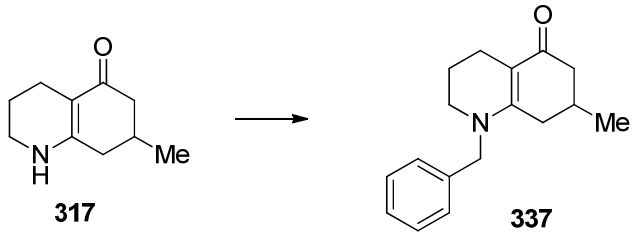
7-Methyl-1,2,3,4,5,6,7,8-octahydroquinolin-5-one (317)



316 **317**

This was performed in accordance with a literature procedure.[124] A solution of 5-methylcyclohexane-1,3-dione **316** (1.20 g, 9.51 mmol, 1.00 equiv), 3-bromopropylammonium bromide **315** (2.17 g, 9.89 mmol, 1.04 equiv) and 2,6-lutidine (2.94 g, 3.2 mL, 27.5 mmol, 3.00 equiv) in EtOH (6 mL) was heated at 130 °C for 20 min in a microwave reactor. The reaction mixture was quenched by addition of aq. NaOH solution (1.0 M, 50 mL) and extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and concentrated to 5 mL. Acetonitrile (2 × 30 mL) was added and the resulting solution was concentrated again to give the crude. Purified by column chromatography (100% EtOAc to 100:1:1 (EtOAc:Et_3N:MeOH)) in petroleum ether) to give the title product **317** (1.52g, 97%) as beige solid; R_f 0.17 (100% EtOAc in petroleum ether). Analytical data were consistent with those previously reported:[124] m.pt. 173–174 °C; δ_H (400 MHz, $CDCl_3$) 4.56 (1H, br s), 3.32-3.20 (2H, m), 2.41 (1H, dd, *J* 17.0, 3.0 Hz), 2.34 (1H, app t, *J* 6.0 Hz,), 2.22-2.07 (3H, m), 2.02 (1H, dd, *J* 17.0, 11.0 Hz), 1.86-1.73 (2H, m), 1.04 (3H, d, *J* 6.0, Hz, -CH(C*H*$_3$)-); δ_C (100 MHz, $CDCl_3$) 194.2 (>C=O), 158.6 (4°), 104.2 (4°), 44.8 (2°), 41.5 (2°), 37.5 (2°), 29.0 (3°), 21.2 (2°), 21.1 (2°), 18.9 (1°).

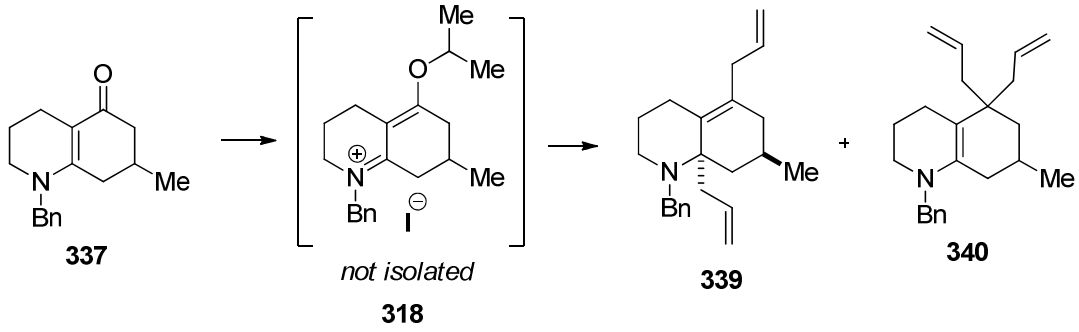
1-Benzyl-7-methyl-1,2,3,4,5,6,7,8-octahydroquinolin-5-one (337)



This was performed by adaptation of a literature procedure.[124] To a suspension of NaH (60% in mineral oil, 0.950 g, 23.8 mmol, 2.50 equiv) in THF (10 mL), a solution of vinylogous amide **317** (1.57 g, 9.50 mmol, 1.00 equiv) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 10 min, then benzyl bromide (2.82 mL, 23.7 mmol, 2.50 equiv) was added dropwise. Then reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was quenched by addition of water and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated Under reduced pressure, then purified by column chromatography (75% EtOAc in petrol to 100:1:5 (EtOAc:Et_3N:MeOH)) to give the title product **337** (1.77 g, 73%) as brown oil: R_f 0.32 (100:1:5 (EtOAc:Et_3N:MeOH));. δ_H (250 MHz, $CDCl_3$) 7.46-7.27 (3H, m, Ar-*H*), 7.20-7.06 (2H, m, Ar-*H*), 4.58 (1H, d, *J* 16.5 Hz, >N-C*H*$_2$-C_6H_5), 4.43 (1H, d, *J* 16.5 Hz, >N-C*H*$_2$-C_6H_5), 3.20 (2H, t, *J* 5.5 Hz,-CH_2-C*H*$_2$-N<), 2.60-1.72 (9H, m), 0.98 (3H, d, *J* 6.0 Hz, -CH(C*H*$_3$)-); δ_C (62.5 MHz, $CDCl_3$) 193.8 (-(>N-)C=C-C(O)-), 158.8 (>N-)*C*=C-C(O-)-), 137.0 (Ar 4°), 128.4 (Ar *C*H), 127.3 (Ar *C*H), 125.8 (Ar *C*H), 105.9 (-(>N-)C=*C*-C(O)-), 53.9 (>N-*C*H_2-C_6H_5), 49.4 (-CH_2-CH_2-*C*H_2-N<), 43.9 (-*C*H_2-CH_2-CH_2-N<), 34.7 (-CO-*C*H_2-$CH(CH_3)CH_2$-), 28.8 (-CH_2-*C*$H(CH_3)CH_2$-), 21.2 (-CH_2-CH(*C*H_3)CH_2-), 21.0 (-CH_2-*C*H_2-CH_2-N<), 19.7 (-CH_2-$CH(CH_3)$-*C*H_2-); ν_{max} (film) 2949, 2874, 1604, 1538, 1432, 1394, 1347, 1309, 1242, 1203, 1143, 1078, 1001, 966. 909, 886, 725, 696, 642 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{17}H_{21}NO + Na)^+$, 278.1520, found, 278.1521.

(7R*,8aR*)-1-Benzyl-5,8a-diallyl-7-methyl-1,2,3,4,6,7,8,8a-octahydroquinoline (339)

1-Benzyl-5,5-diallyl-7-methyl-1,2,3,4,5,6,7,8-octahydroquinoline (340)



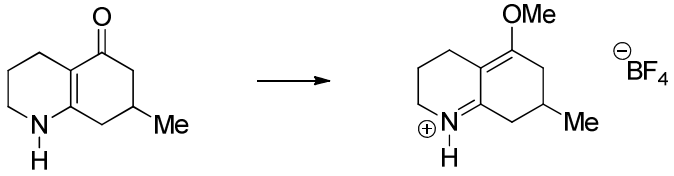
This was performed by adaptation of a literature procedure.[124] To a resealable pressure tube was added vinylogous amide **337** (324 mg, 1.27 mmol, 1.00 equiv) and 2-iodopropane **336** (2.00 mL, 3.45 g, 20.3 mmol, 16.0 equiv). The reaction mixture was sealed and heated at 65 °C for 108 h, then diluted with benzene (2 × 6 mL), and concentrated to remove excess 2-iodopropane to give crude salt **337**. To a solution of the residue (salt **337**) in THF (9 mL) allylmagnesium bromide (0.320 M in Et_2O, 7.14 mL, 2.29 mmol, 1.80 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at the temperature for 1 h before warming to the rt. After further 2 h reaction was quenched by addition of water and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (5 to 10% EtOAc in petrol) to give the title products:

Title compound **339** (70.0 mg, 17%), a brown oil; R_f 0.57 (5% EtOAc in petroleum ether);. δ_H (300 MHz, $CDCl_3$) 7.40-7.19 (5H, m, Ar-*H*), 5.92-5.71 (2H, m, 2 × -CH_2-C*H*=CH_2), 5.11-4.98 (4H, m, 2 × -CH_2-CH=C*H*$_2$), 4.16 (1H, d, *J* 13.5 Hz, >N-C*H*$_2$-C_6H_5), 3.24 (1H, d, *J* 13.5 Hz, >N-C*H*$_2$-C_6H_5), 2.99-2.83 (2H, m), 2.78-2.44 (5H, m), 2.16-1.25 (8H, m), 0.92 (3H, d, *J* 6.0 Hz, -CH(C*H*$_3$)-); δ_C (75 MHz, $CDCl_3$) 136.9 (Ar 4°), 136.4 (-CH_2-*C*H=CH_2), 136.2 (-CH_2-*C*H=CH_2),

128.2 (Ar *C*H), 128.1 (Ar *C*H), 128.0 (Ar *C*H), 126.6 (>*C*=C<), 115.8 (-CH_2-CH=*C*H_2), 114.6 (>*C*=C<), 114.4 (-CH_2-CH=*C*H_2), 53.9 (2°), 46.6 (2°), 44.8 (4°), 39.2 (2°), 38.0 (2°), 36.5 (2°), 26.5 (2°), 25.5 (2°), 24.2 (2°), 22.4 (1°), 21.5 (3°); ν_{max} (film) 3075, 2948, 2922, 2865, 2792, 1635, 1493, 1453, 1360, 1282, 1179, 1089, 1027, 992, 906, 871, 803, 731, 696 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{23}H_{31}N + H)^+$, 322.2529, found, 322.2548.

Title compound **340** (22.0 mg, 5%), a light brown oil; R_f 0.40 (5% EtOAc in petroleum ether); δ_H (250 MHz, $CDCl_3$) 7.36-7.21 (5H, m, Ar-*H*), 5.90-5.63 (2H, m, 2 × -CH_2-C*H*=CH_2), 5.17-4.96 (4H, m, 2 × -CH_2-CH=C*H*$_2$), 4.10 (2H, s, >N-C*H*$_2$-C_6H_5), 2.98-2.77 (2H, m), 2.33-0.94 (13H, m), 0.89 (3H, d, *J* 6.5 Hz, -CH(C*H*$_3$)-); δ_C (62.5 MHz, $CDCl_3$) 140.5 (Ar 4°), 138.0 (>*C*=C<), 136.5 (-CH_2-*C*H=CH_2), 136.4 (-CH_2-*C*H=CH_2), 128.2 (Ar *C*H), 127.4 (Ar *C*H), 126.5 (Ar *C*H), 116.3 (-CH_2-CH=*C*H_2), 116.0 (-CH_2-CH=*C*H_2), 110.2 (>*C*=C<), 53.9 (2°), 48.5 (2°), 44.4 (2°), 43.1 (2°), 41.2 (2°), 36.4 (2°), 29.6 (4°), 25.0 (2°), 22.3 (2°), 22.1 (1°), 21.7 (3°); ν_{max} (film) 3073, 2923, 2854, 1634, 1494, 1452, 1373, 1320, 1183, 1108, 1072, 1028, 994, 966, 907, 730, 697 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{23}H_{31}N + H)^+$, 322.2529, found, 322.2534.

5-Methoxy-7-methyl-2,3,4,6,7,8-hexahydroquinolin-1-ium tetrafluoroborate (341)



317 **341**

To a suspention of Meerwein's salt **342** (560 mg, 3.81 mmol, 1.05 equiv) in DCM (15 mL) was added vinylogous amide **317** (600 mg, 3.63 mmol, 1.00 equiv) in DCM (10 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction solvent was removed under

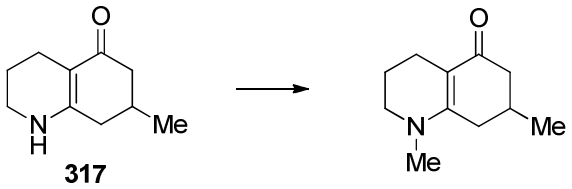
reduced pressure to give crude product **341** (703 mg, 98%) as pale yellow oil of two rotamers: δ_H (250 MHz, $CDCl_3$) 8.77 (1H, br s, $>N^+(H)=$), 3.89 (3H, s, $-OCH_3$), 3.42-3.34 (2H, m, $-CH_2-N^+(H)=$), 2.77 (1H, dd, *J* 12.5, 4.5 Hz, $>C(OCH_3)-CH_2-CH(CH_3)-$), 2.57 (1H, dd, *J* 12.5, 4.5 Hz, $>C(OCH_3)-CH_2-CH(CH_3)-$), 2.32-2.06 (5H, m), 1.78-1.70 (2H, m, $-CH_2-CH(CH_3)-CH_2-$), 1.00 (3H, d, *J* 5.5 Hz $-CH_2-CH(CH_3)-$);

Major rotamer: δ_C (100 MHz, $CDCl_3$) 180.2 ($-N^+(H)=C<$), 174.0 ($=C(OCH_3)-CH_2-CH(CH_3)-$), 105.8 ($>C=C(OCH_3)-CH_2-$), 56.9 ($=C(OCH_3)-CH_2-$), 42.6 ($-CH_2-N^+(H)=$), 36.1 ($=C(OCH_3)-CH_2-$), 32.7 ($-CH_2-CH(CH_3)-$), 27.7 (2°), 19.7 (1°), 18.7 (2°), 17.8 (2°);

Minor rotamer: δ_C (100 MHz, $CDCl_3$) 178.2 ($-N^+(H)=C<$), 174.7 ($=C(OCH_3)-CH_2-CH(CH_3)-$), 103.8 ($>C=C(OCH_3)-CH_2-$), 53.3 ($=C(OCH_3)-CH_2-$), 42.7 ($-CH_2-N^+(H)=$), 36.8 ($-CH_2-CH(CH_3)-$), 36.5 ($=C(OCH_3)-CH_2-$), 27.8 (2°), 19.6 (2°), 18.7 (1°), 17.5 (2°);

ν_{max} (film) 3250, 2988, 2885, 1651, 1483, 1383, 1314, 1273, 1183, 1140, 1005, 946 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{11}H_{17}NO + H)^+$, 180.1383, found, 180.1520.

1,7-Dimethyl-1,2,3,4,5,6,7,8-octahydroquinolin-5-one (323)

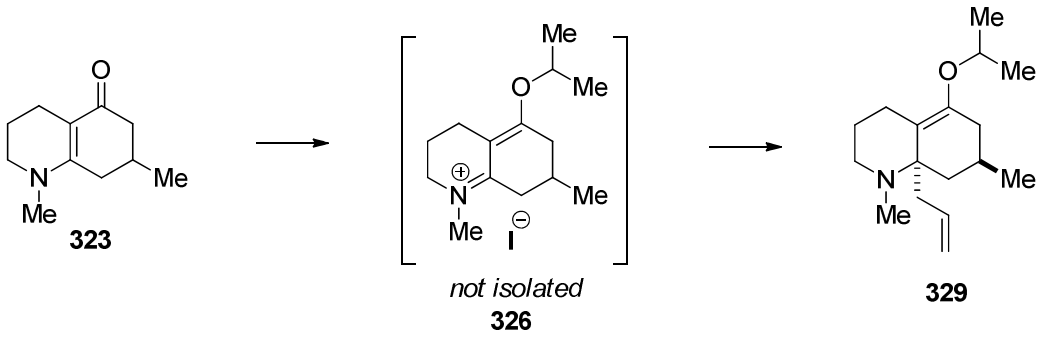


317 **323**

This was performed in accordance with a literature procedure.[124] To a suspension of NaH (60% in mineral oil, 330 mg, 8.32 mmol, 1.25 equiv) in THF (10 mL), a solution of vinylogous amide **317** (1.10 g, 6.66 mmol, 1.00 equiv) in THF (15 mL) was added dropwise at 0 °C. The reaction mixture was stirred for

20 min and MeI (1.53 mL, 9.99 mmol, 1.50 equiv) was added dropwise. Then reaction mixture was allowed to warm to rt and stirred for 14 h. The reaction mixture was quenched by addition of water and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (100% EtOAc in petrol to 100:1:1 (EtOAc:Et_3N:MeOH)) to give the title product **323** (780 mg, 66%) as light yellow-brown oil: R_f 0.12 (100:1:1 (EtOAc:Et_3N:MeOH)). Analytical data were consistent with those previously reported:[124] δ_H (400 MHz, $CDCl_3$) 3.24-3.17 (2H, m), 2.99 (3H, s), 2.55 (1H, dd, *J* 16.0, 4.0 Hz), 2.46-2.23 (3H, m), 2.16-1.94 (3H, m), 1.80-1.71 (2H, m), 1.06 (3H, d, *J* 6.0, Hz); δ_C (100 MHz, $CDCl_3$) 193.4 (>C=O), 159.6 (4°), 105.6 (4°), 51.3 (2°), 43.9 (2°), 38.5 (1°), 35.1 (2°), 28.8 (2°), 21.5 (2°), 21.1 (2°), 19.5 (1°).

(7S*,8aR*)-8a-Allyl-5-isopropoxy-1,7-dimethyl-1,2,3,4,6,7,8,8a-octahydroquinoline (329)

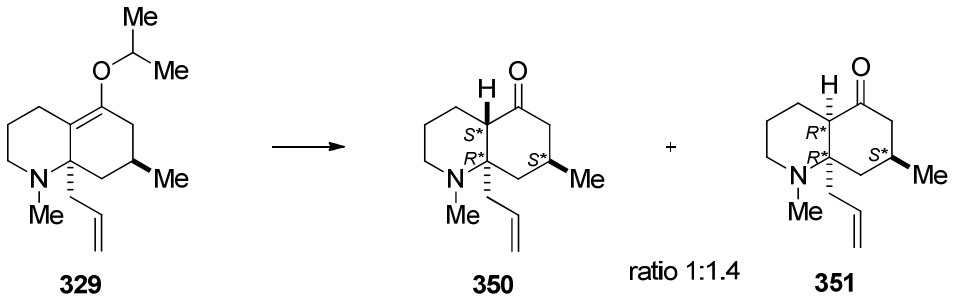


This was performed in accordance with a literature procedure.[124] To a resealable pressure tube was added vinylogous amide **323** (788 mg, 4.39 mmol, 1.00 equiv) and 2-iodopropane **336** (6.00 mL, 10.2 g, 60.1 mmol, 13.6 equiv). The reaction mixture was sealed and heated at 65 °C for 108 h, diluted with benzene (2 × 12 mL), and concentrated to remove excess 2-iodopropane to give crude salt **326**. To a solution of the residue (salt **326**) in THF (25 mL)

allylmagnesium bromide (0.990 M in Et_2O, 5.55 mL, 5.50 mmol, 1.25 equiv) was added dropwise at –78 °C. The reaction mixture was stirred at the temperature for 1 h before warming it up to the rt. After a further 2 h, the reaction mixture was quenched by addition of water and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give the crude product **329** (767 mg, 67%) as a brown oil; δ_H (250 MHz, $CDCl_3$) 5.07-5.53 (1H, m, -CH_2-C*H*=CH_2), 4.88 (1H, d, J_{trans} 17.0 Hz, -CH_2-CH=C*H*$_2$), 4.81 (1H, d, J_{cis} 10.0 Hz, -CH_2-CH=C*H*$_2$), 3.95 (1H, hept, *J* 6.0 Hz, -O-C*H*$(CH_3)_2$), 2.98-2.46 (4H, m), 2.26-2.13 (1H, m), 2.19 (3H, s, >N-C*H*$_3$), 1.97-1.43 (6H, m), 1.30-1.13 (2H, m), 1.07 (3H, d, *J* 6.0 Hz, -O-CH(C*H*$_3)_2$), 1.03 (3H, d, *J* 6.0 Hz, -O-CH(C*H*$_3)_2$), 0.79 (3H, d, *J* 6.0 Hz, -CH_2-CH(C*H*$_3$)-CH_2-); δ_C (62.5 MHz, $CDCl_3$) 145.6 (>C=*C*$(OCH(CH_3)_2)$-), 136.2 (-CH_2-*C*H=CH_2), 119.5 (>*C*=C$(OCH(CH_3)_2)$-), 115.5 (-CH_2-CH=*C*H_2), 77.2 (-O-*C*H$(CH_3)_2$), 68.2 (-*C*H_2-N(CH_3)-), 59.5 (>*C*-CH_2-CH(CH_3)-), 50.3 (-*C*H_2-CH(CH_3)-CH_2-), 44.5 (-CH_2-*C*H(CH_3)-CH_2-), 37.6 (-*C*H_2-CH=CH_2), 34.3 (2°), 33.9 (2°), 25.4 (2°), 22.7 (2°), 21.9 (-O-CH(*C*$H_3)_2$), 21.9 (-O-CH(*C*$H_3)_2$), 20.4 (-CH_2-CH(*C*H_3)-CH_2-); ν_{max} (film) 2925, 2868, 2787, 1671, 1604, 1555, 1453, 1370, 1307, 1279, 1149, 1114, 1057, 1001, 993, 916, 864, 791, 743, 669 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{17}H_{29}NO$ - $(CH_3)_2CHOH$ + H_2O + $Na)^+$, 244.1677, found, 244.1686.

(4aS*,7S*,8aR*)-8a-Allyl-1,7-dimethyldecahydroquinolin-5-one (350)

(4aR*,7S*,8aR*)-8a-Allyl-1,7-dimethyldecahydroquinolin-5-one (351)



329 **350** ratio 1:1.4 **351**

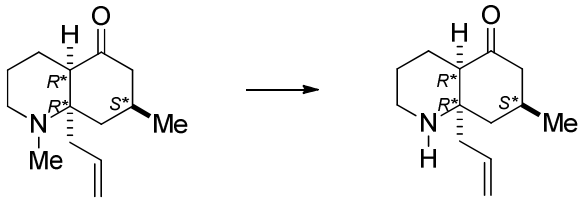
This was performed in accordance with a literature procedure.[124] To a solution of **329** (767 mg, 2.91 mmol, 1.00 equiv) in Et_2O (20 mL) aq. H_2SO_4 (1.00 N, 20 mL) was added and the resulting mixture was stirred at rt for 3 h. The ethereal layer was separated and the aqueous layer extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2 × 30 mL) then brine (50 mL), dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, then purified by column chromatography (25:75:0:0 to 0:100:10:5 (Petrol:EtOAc:Et_3N:MeOH)) to give the title products:

Product **350** (66.0 mg, 7%), a light yellow-brown oil; R_f 0.47 (50:50:1:1 (Petrol:EtOAc:Et_3N:MeOH)); δ_H (500 MHz, $CDCl_3$) 5.87-5.78 (1H, m, -CH_2-C*H*=CH_2), 5.03-4.99 (2H, m, -CH_2-CH=C*H*$_2$), 2.81-2.74 (2H, m, -N(CH_3)-C*H*$_2$-CH_2-CH_2-CH< and -C*H*$_2$-CH=CH_2), 2.61-2.58 (1H, m, -N(CH_3)-C*H*$_2$-CH_2-CH_2-CH<), 2.45 (1H, dd, *J* 12.0, 3.0 Hz, >C*H*-C(O)-CH_2-CH<), 2.42 (3H, s, >N-C*H*$_3$), 2.35-2.32 (1H, m), 2.25-2.22 (1H, m, >CH-C(O)-C*H*$_2$-CH<), 2.03-1.97 (2H, m, >C*H*(CH_3) and >CH-C(O)-C*H*$_2$-CH<), 1.67-1.47 (5H, m), 1.38 (1H, t, *J* 12.0 Hz, >CH-C(O)-C*H*$_2$-CH<), 1.02 (3H, d, *J* 6.0 Hz, -O-CH(C*H*$_3$)$_2$); δ_C (125 MHz, $CDCl_3$) 211.3 (>CO), 134.5 (-CH_2-*C*H=CH_2), 117.4 (-CH_2-CH=*C*H_2), 61.6 (>*C*-CH_2-CH(CH_3)-), 55.4 (>*C*H-C(O)-CH_2-), 49.2 (-CH_2-CH_2-*C*H_2-N(CH_3)-), 49.0 (>CH-C(O)-*C*H_2-CH<), 42.2 (-*C*H_2-CH(CH_3)-CH_2-C(O)-), 38.5 (>N-*C*H_3), 30.6 (-*C*H_2-CH=CH_2), 28.1 (-CH_2-*C*H(CH_3)-CH_2-C(O)-), 23.0 (-CH_2-*C*H_2-CH_2-N(CH_3)-), 22.6 (-CH(*C*H_3)), 18.6 (-*C*H_2-CH_2-CH_2-N(CH_3)-); ν_{max} (film) 2927, 2867, 2793,

1705, 1638, 1456, 1443, 1331, 1300, 1270, 1143, 1040, 991, 911 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{14}H_{23}NO + Na)^+$, 244.1677, found, 244.1686.

Product **351** (95.0 mg, 10%), a light yellow-brown oil; R_f 0.16 (50:50:1:1 (Petrol:EtOAc:Et_3N:MeOH)); δ_H (500 MHz, $CDCl_3$) 5.84 (1H, ddt, *J* 17.0, 10.0, 7.0 Hz,-CH_2-C*H*=CH_2), 5.09 (1H, dd, J_{cis} 10.0, 1.0 Hz, -CH_2-CH=C*H*$_2$), 5.01 (1H, dd, J_{trans} 17.0, 1.0 Hz, -CH_2-CH=C*H*$_2$), 2.63-2.53 (2H, m, -N(CH_3)-C*H*$_2$-CH_2-CH_2-CH<), 2.47 (1H, dd, *J* 8.5, 7.5 Hz, >C*H*-C(O)-CH_2-), 2.30-2.25 (1H, m, -C*H*$_2$-CH=CH_2), 2.23 (3H, s, >N-C*H*$_3$), 2.18 (1H, dd, *J* 14.5, 5.0 Hz, >CH-C(O)-C*H*$_2$-CH<), 2.09 (1H, dd, *J* 14.5, 12.0 Hz, >CH-C(O)-C*H*$_2$-CH<), 1.99 (1H, dd, *J* 15.0, 7.5 Hz, -C*H*$_2$-CH=CH_2), 1.90-1.81 (1H, m, -CH_2-C*H*(CH_3)-CH_2-), 1.75 (1H, app t, *J* 13.0 Hz, -C*H*$_2$-CH(CH_3)-CH_2-C(O)-), 1.65-1.60 (3H, m), 1.55-1.48 (2H, m), 1.03 (3H, d, *J* 6.0 Hz, -CH(C*H*$_3$)); δ_C (125 MHz, $CDCl_3$) 214.0 (>CO), 133.0 (-CH_2-*C*H=CH_2), 117.8 (-CH_2-CH=*C*H$_2$), 59.4 (>*C*-CH_2-CH(CH_3)-), 53.7 (>*C*H-C(O)-CH_2-), 49.5 (-CH_2-CH_2-*C*H$_2$-N(CH_3)-), 45.2 (>CH-C(O)-*C*H$_2$-CH<), 40.4 (-*C*H$_2$-CH=CH_2), 37.0 (>N-*C*H$_3$), 29.9 (-*C*H$_2$-CH(CH_3)-CH_2-C(O)-), 27.1 (-CH_2-*C*H(CH_3)-CH_2-C(O)-), 25.8 (-CH_2-*C*H$_2$-CH_2-N(CH_3)-), 24.6 (-*C*H$_2$-CH_2-CH_2-N(CH_3)-), 22.5 (-CH(*C*H$_3$)); ν_{max} (film) 2927, 2867, 2793, 1705, 1638, 1456, 1443, 1331, 1300, 1270, 1143, 1040, 991, 911 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{14}H_{23}NO + Na)^+$, 244.1677, found, 244.1686.

(4aR*,7S*,8aR*)-8a-Allyl-7-methyldecahydroquinolin-5-one (361).



351 **361**

A stirred solution of allyl ketone **351** (110 mg, 0.490 mmol 1.00 equiv) and TPP (7.0 mg, 2.5 mol%) in 5 mL of dry DCM in a microwave vial, was irradiated using 2 × 150 watt lamps, while oxygen was bubbled through the purple

solution. The progress of the reaction was monitored by ^{1}H-NMR, after 2 h NMR indicated that the reaction was complete. The reaction mixture was transferred to a round bottom flask and solvent was removed under reduced pressure. The crude residue was purified by column chromatography (50% EtOAc in petroleum ether, then EtOAc:petroleum ether:MeOH:Et_3N (50:50:1:1) to give the title compound **361** as a pale amber oil (35.0 mg, 34%); R_f 0.18 (50:50:1:1 EtOAc:petroleum ether:MeOH:Et_3N); δ_H (500 MHz, $CDCl_3$) 5.78 (1H, ddt, *J* 17.0, 9.5, 7.5 Hz,-CH_2-C*H*=CH_2),, 5.12 (1H, d, J_{cis} 10.0 Hz, -CH_2-CH=C*H*$_2$); 5.08 (1H, d, J_{trans} 17.0, -CH_2-CH=C*H*$_2$), 2.92-2.83 (2H, m, -CH_2-C*H*$_2$-NH-), 2.18-2.08 (4H, m), 2.04-1.90 (4H, m), 1.77-1.63 (2H, m), 1.39-1.25 (3H, m), 1.02 (3H, d, *J* 6.0 Hz, >CH-C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 214.2 (>C=O), 132.0 (-CH_2-*C*H=CH_2), 119.4 (-CH_2-CH=*C*H$_2$), 56.8 (-C*H*-C=O), 55.4 (N-*C*-CH_2-CH=CH_2), 44.9 (-*C*H$_2$-CH=CH_2), 44.6 (-C(O)-*C*H$_2$-CH(CH_3)-), 40.1 (-CH_2-*C*H$_2$-NH-), 35.6 (2°), 27.2 (-CH_2-*C*H(CH_3)-), 25.6 (2°), 25.5 (2°), 22.4 (-CH(*C*H$_3$)-); ν_{max} (film) 3333, 2925, 2854, 1704, 1638, 1455, 1438, 1362, 1264, 1228, 1183, 999 cm^{-1}; TOF-ESI+ *m/z* calculated for $(C_{13}H_{21}NO + H)^+$, 208.1696, found, 208.1835.

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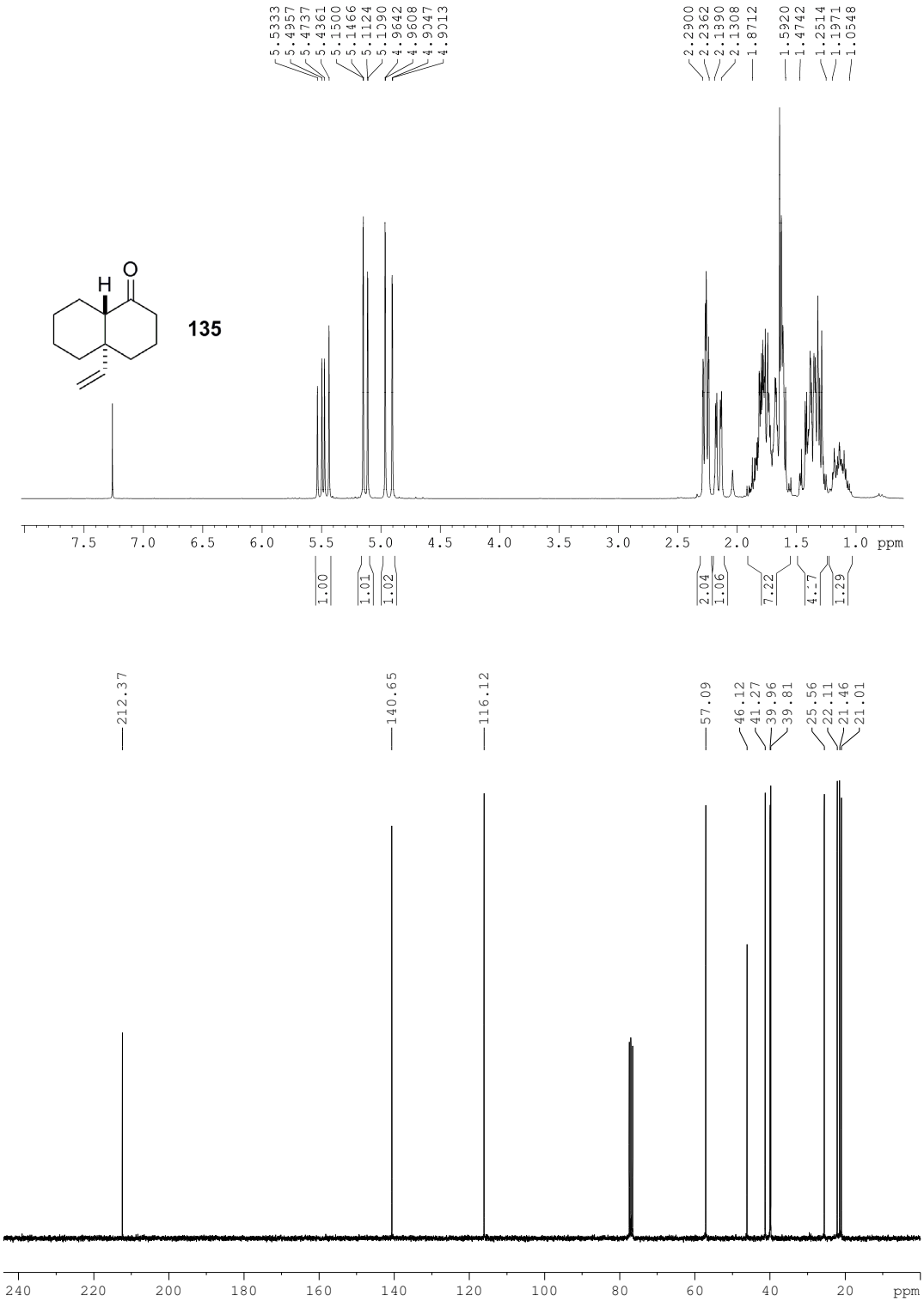
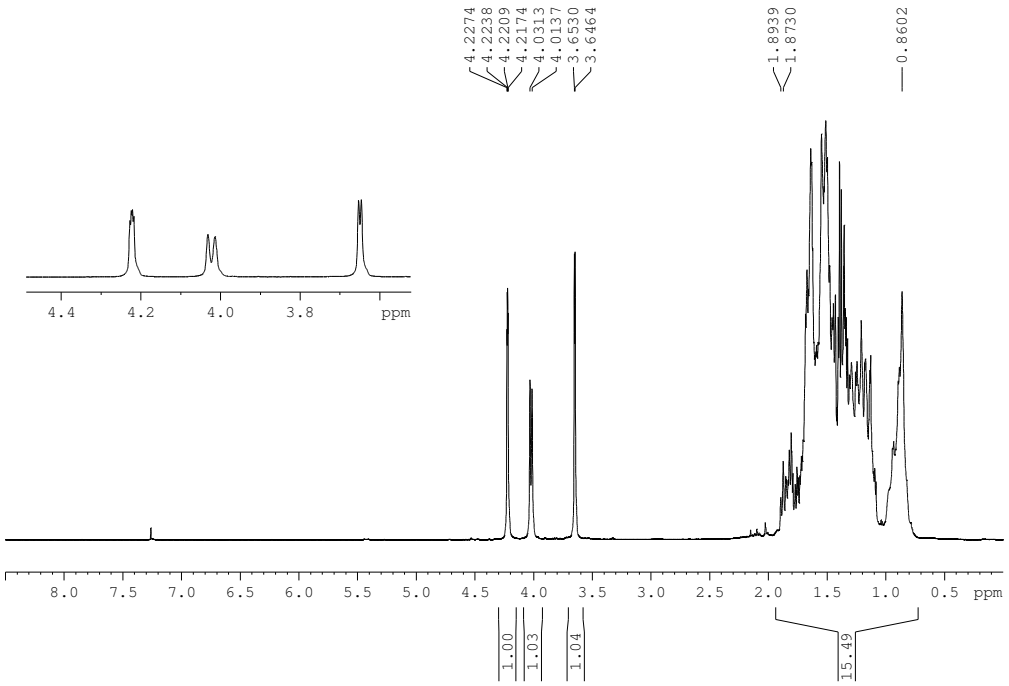
6. APPENDICES

6.1 Selected NMR spectra

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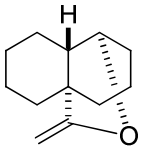
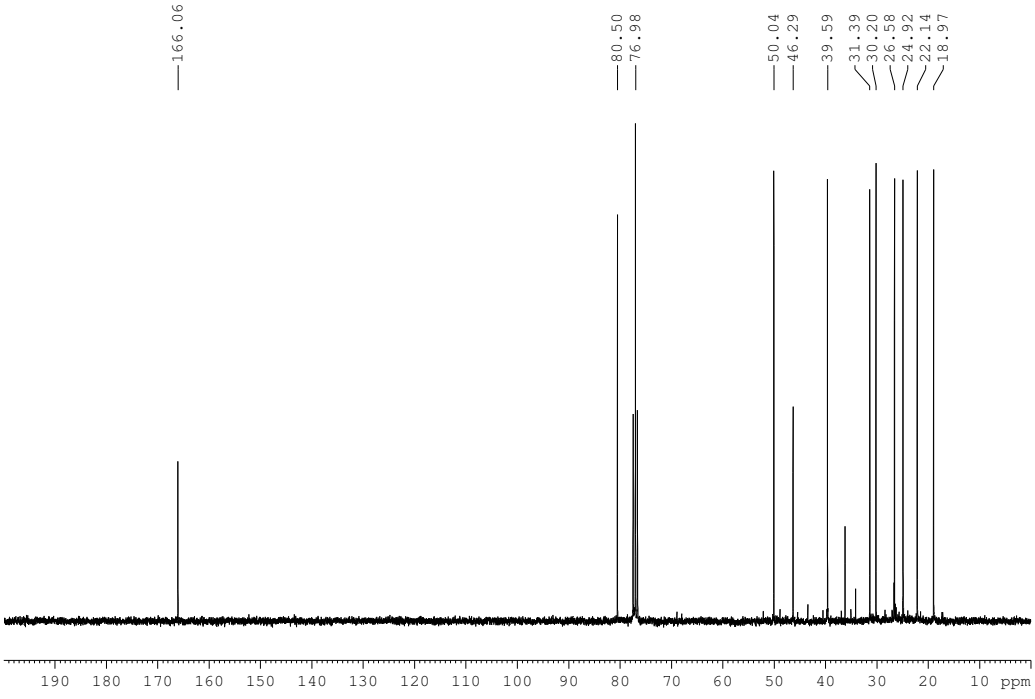
1.8939
1.8730
0.8602
4.4
4.2
4.0
3.8
ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.03
1.04
15.49


H
O

176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80.50
76.98
50.04
46.29
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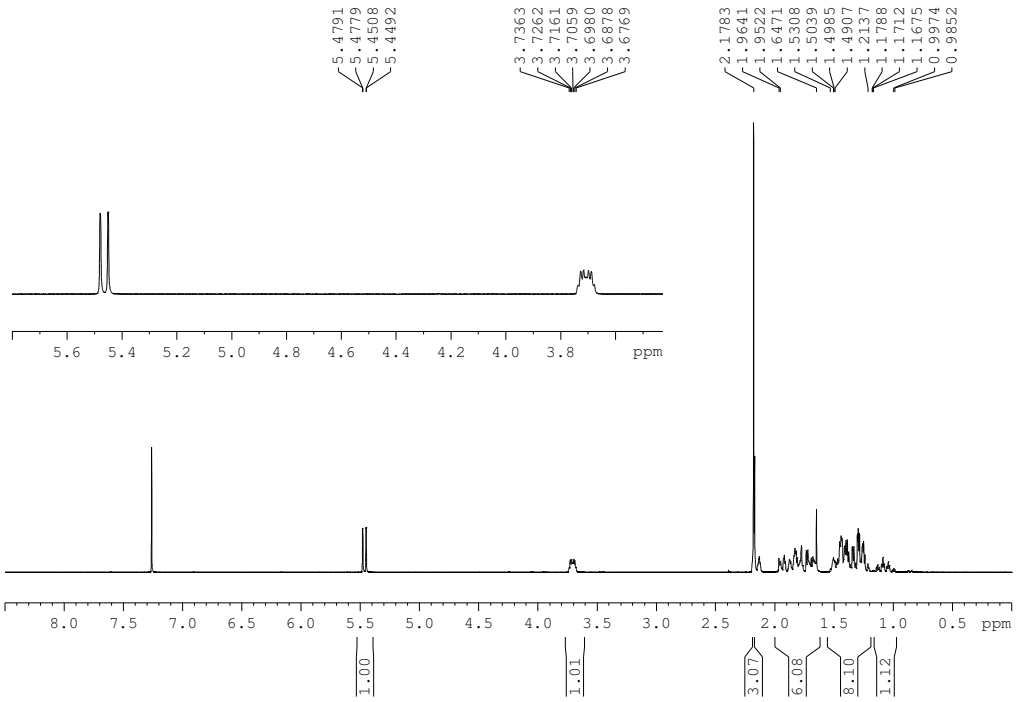
26.58
24.92
22.14
18.97
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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3.6980
3.6878
3.6769
2.1783
1.9641
1.9522
1.6471
1.5308
1.5039
1.4985
1.4907
1.2137
1.1788
1.1712
1.1675
0.9974
0.9852
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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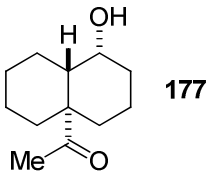
6.08
8.10
1.12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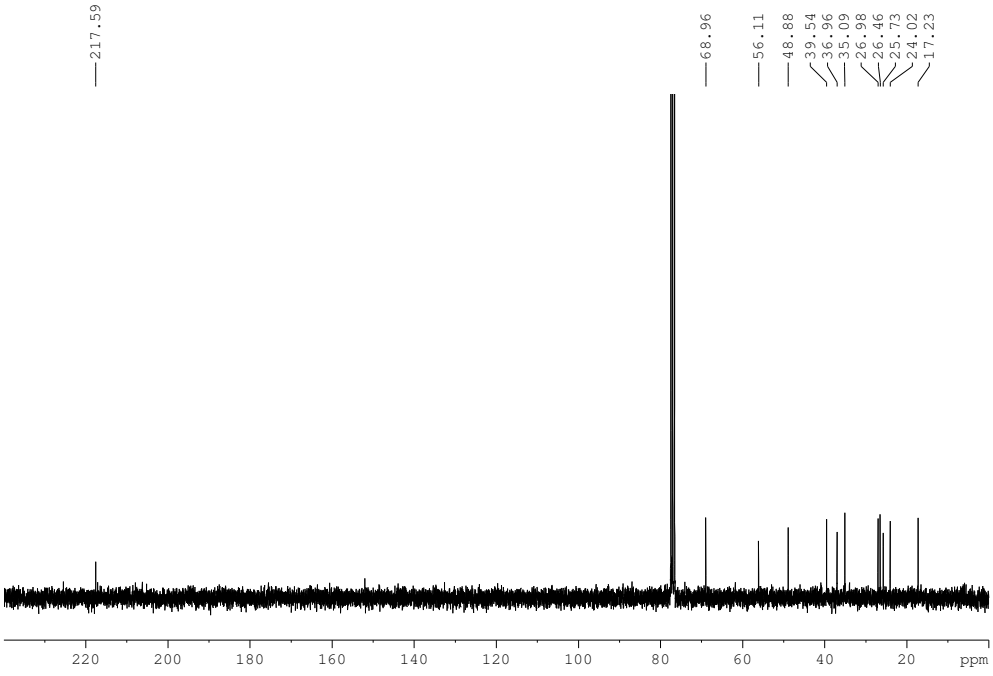
Me
O

177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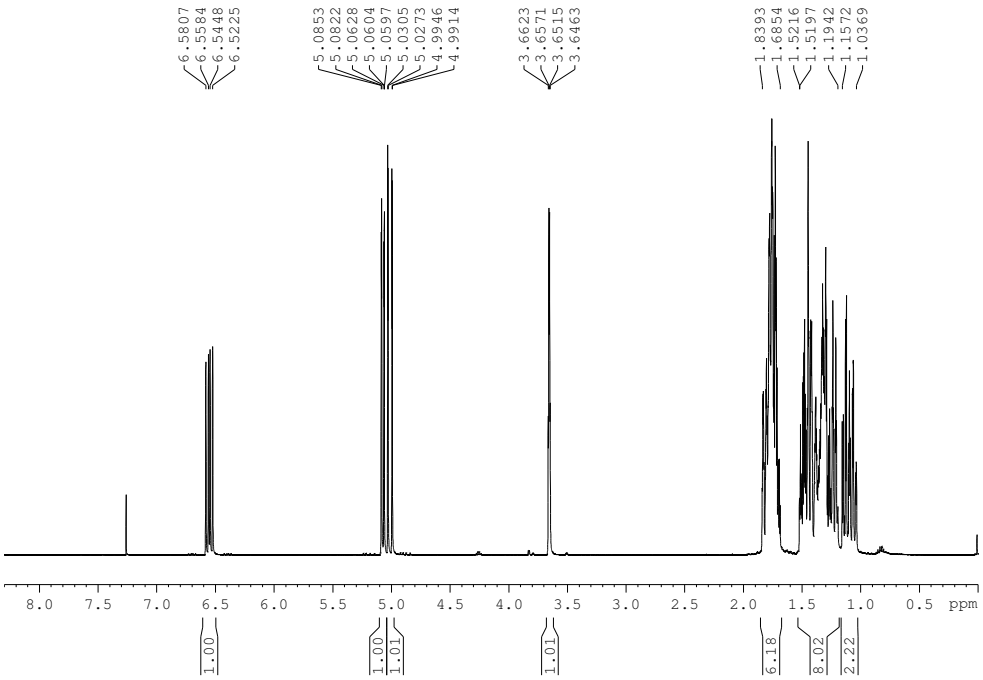
17.23
220 200 180 160 140 120 100 80 60 40 20 ppm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5.0597
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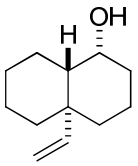
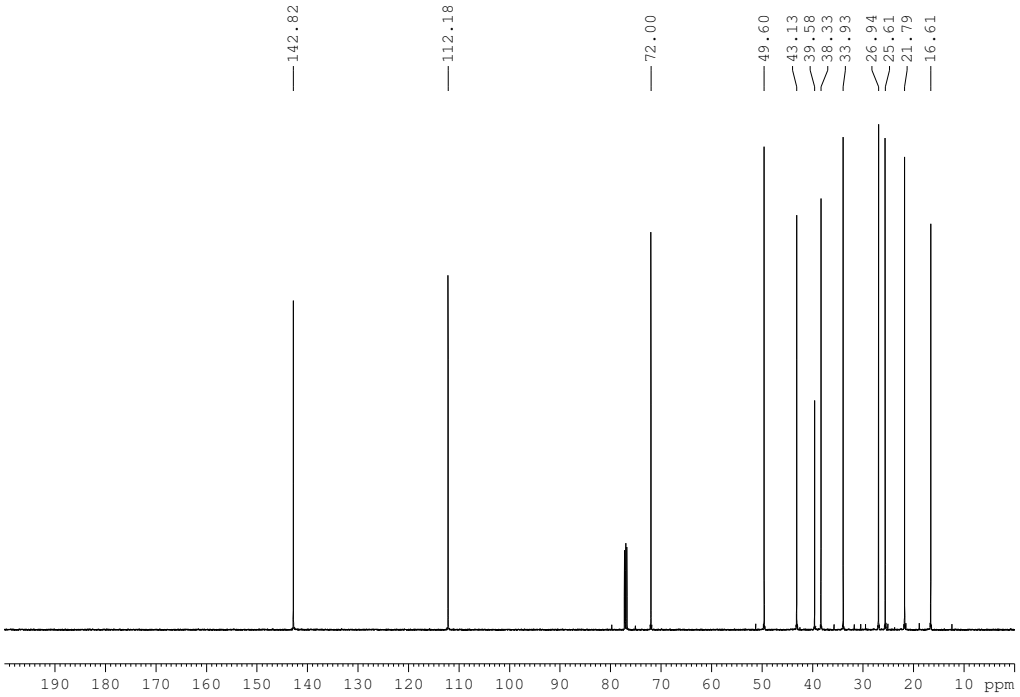
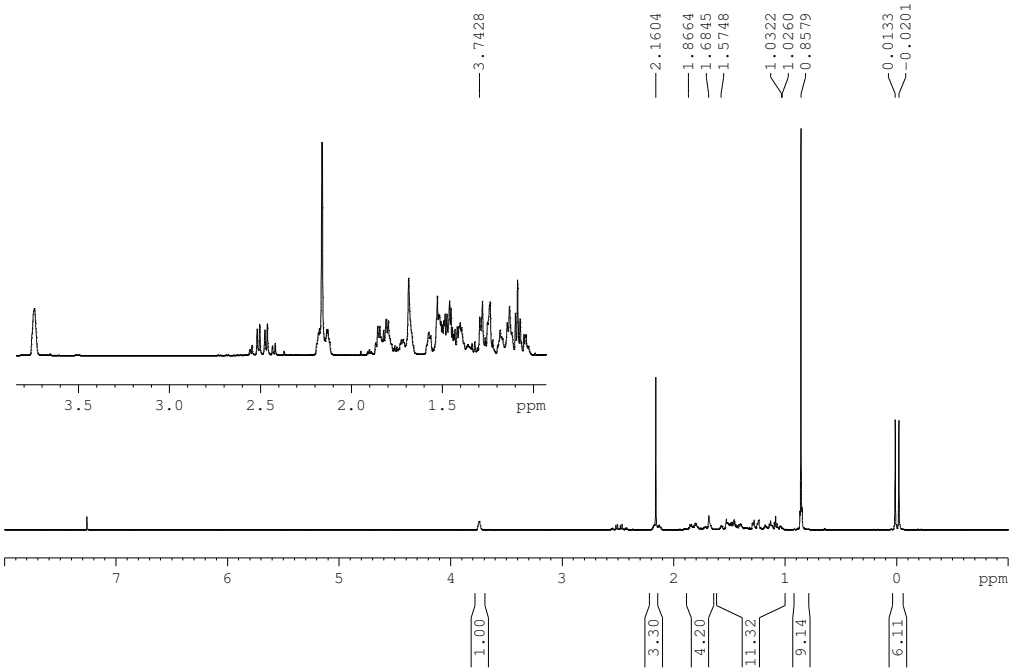
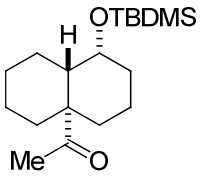
5.0273
4.9946
4.9914
3.6623
3.6571
3.6515
3.6463
1.8393
1.6854
1.5216
1.5197
1.1942
1.1572
1.0369
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.00
1.01
1.01
6.18
8.02
2.22


H
OH

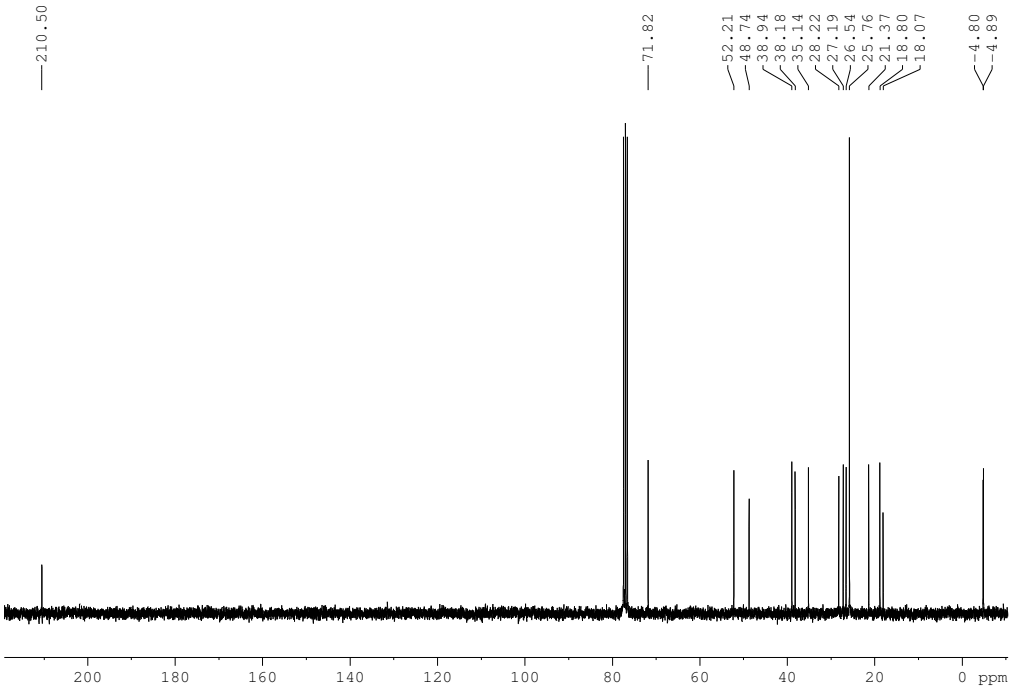
182

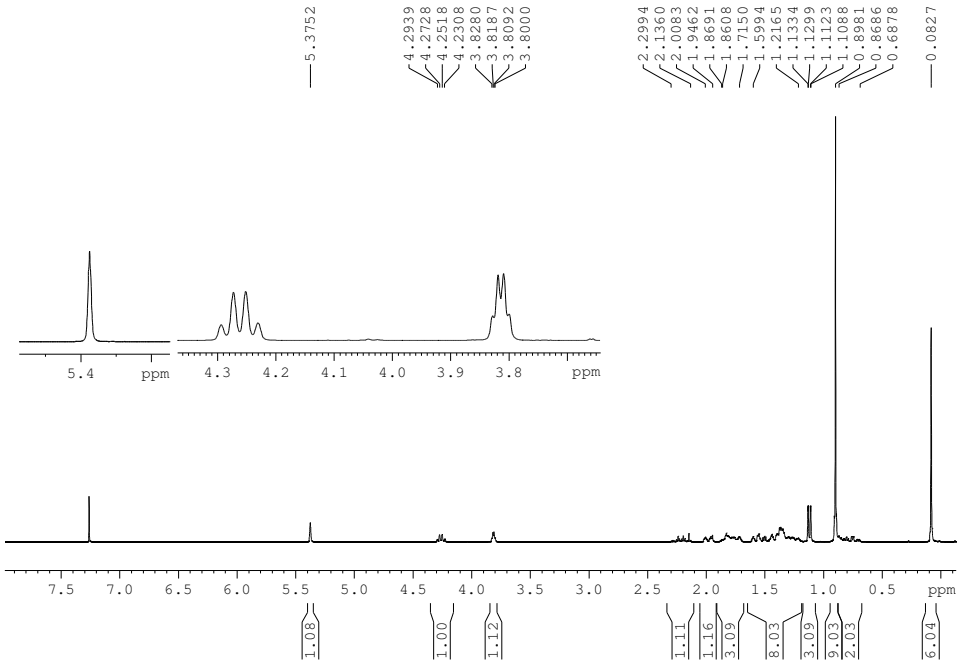

142.82
112.18
72.00
49.60
43.13
39.58
38.33
33.93
26.94
25.61
21.79
16.61
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

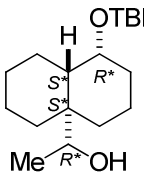

3.7428
2.1604
1.8664
1.6845
1.5748
1.0322
1.0260
0.8579
0.0133
-0.0201
3.5
3.0
2.5
2.0
1.5
ppm
7
6
5
4
3
2
1
0
ppm
1.00
3.30
4.20
11.32
9.14
6.11


OTBDMS
H
Me
O

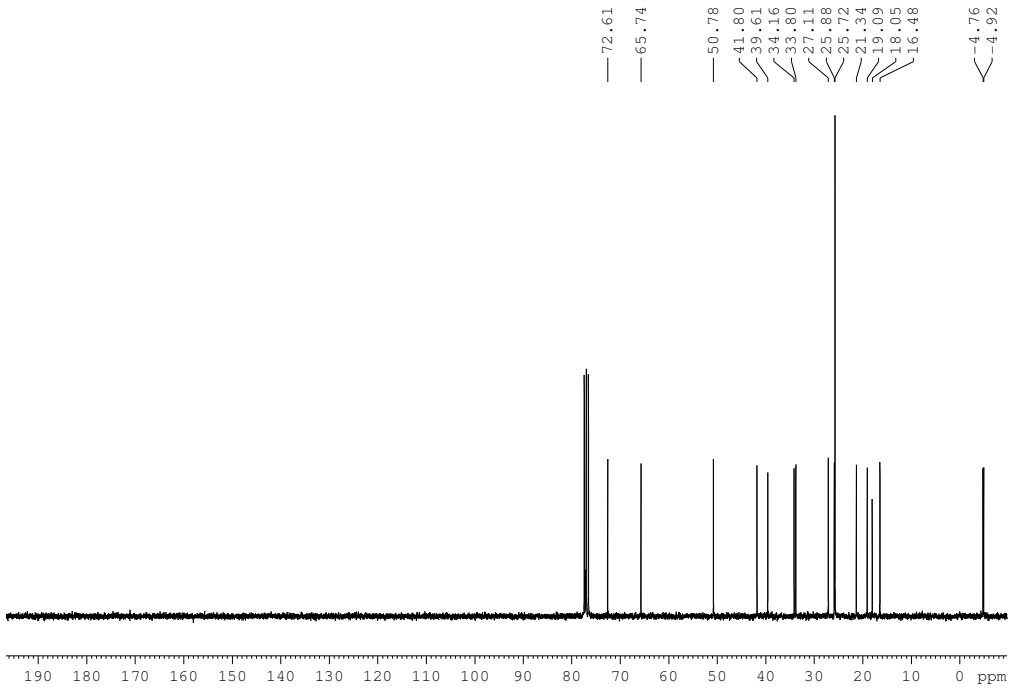
191

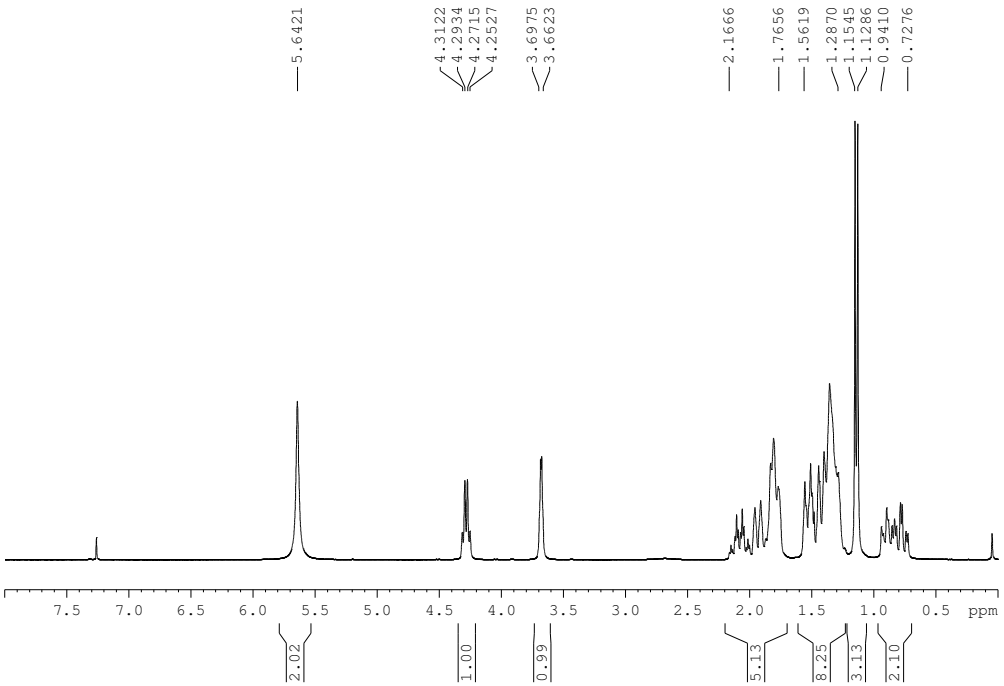

210.50
71.82
52.21
48.74
38.94
38.18
35.14
28.22
27.19
26.54
25.76
21.37
18.80
18.07
-4.80
-4.89
200
180
160
140
120
100
80
60
40
20
0 ppm

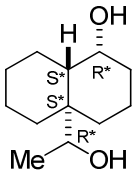

5.3752
4.2939
4.2728
4.2518
4.2308
3.8280
3.8187
3.8092
3.8000
2.2994
2.1360
2.0083
1.9462
1.8691
1.8608
1.7150
1.5994
1.2165
1.1334
1.1299
1.1123
1.1088
0.8981
0.8686
0.6878
0.0827
5.4 ppm
4.3 4.2 4.1 4.0 3.9 3.8 ppm
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.08
1.00
1.12
1.11
1.16
3.09
8.03
3.09
9.03
2.03
6.04


OTBDMS
H
S*
S*
R*
Me
R*
OH

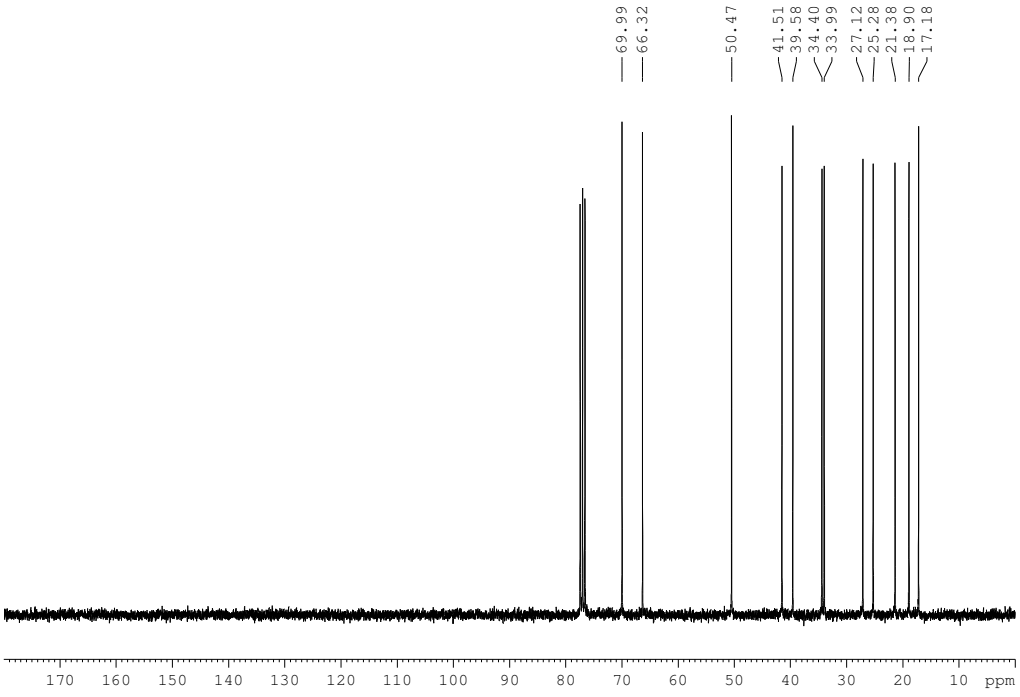
192

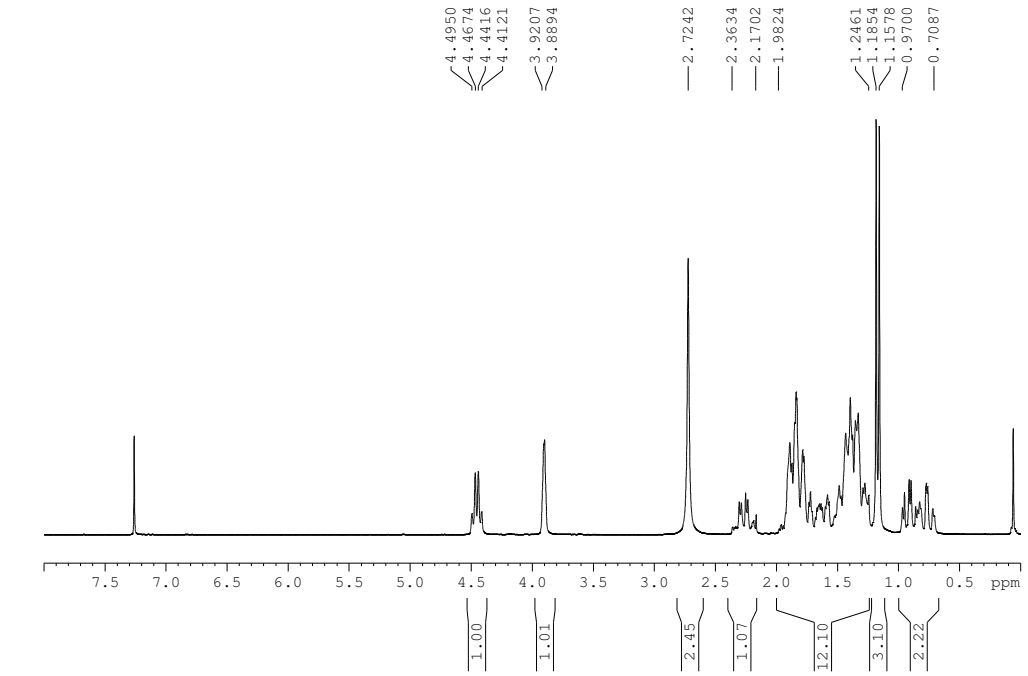

72.61
65.74
50.78
41.80
39.61
34.16
33.80
27.11
25.88
25.72
21.34
19.09
18.05
16.48
-4.76
-4.92
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

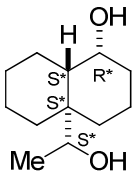

5.6421
4.3122
4.2934
4.2715
4.2527
3.6975
3.6623
2.1666
1.7656
1.5619
1.2870
1.1545
1.1286
0.9410
0.7276
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.02
1.00
0.99
5.13
8.25
3.13
2.10


OH
H
S*
R*
S*
R*
Me
OH

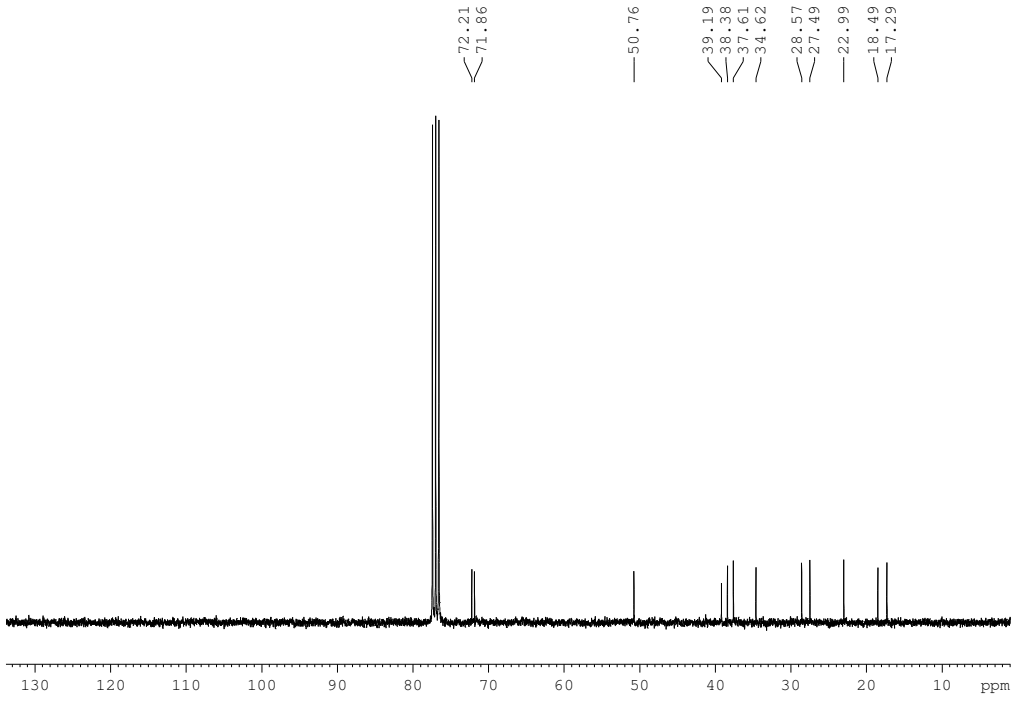
193

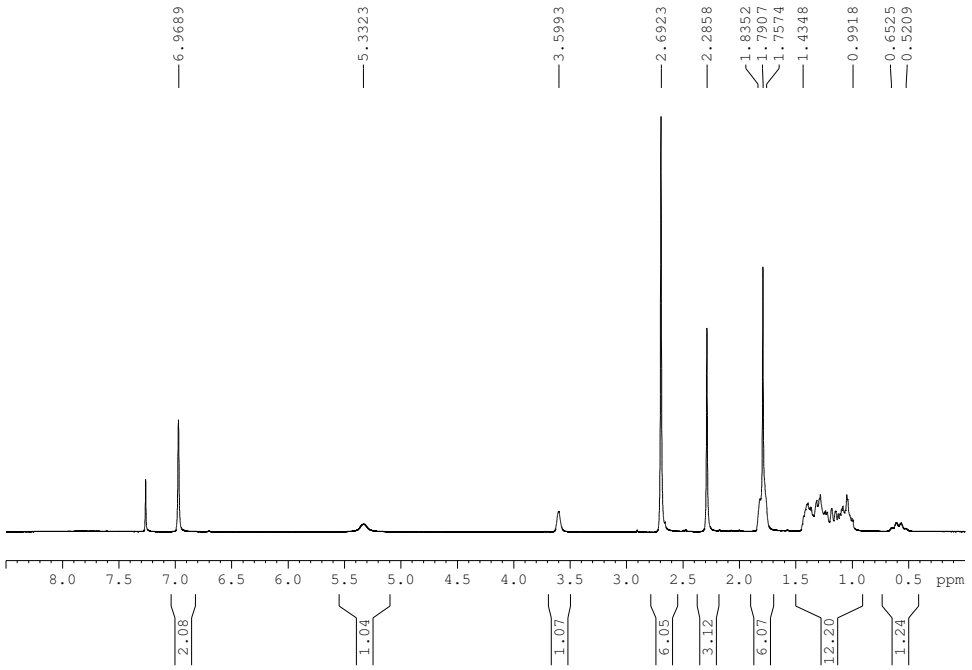

69.99
66.32
50.47
41.51
39.58
34.40
33.99
27.12
25.28
21.38
18.90
17.18
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

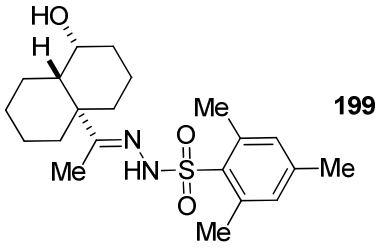

4.4950
4.4674
4.4416
4.4121
3.9207
3.8894
2.7242
2.3634
2.1702
1.9824
1.2461
1.1854
1.1578
0.9700
0.7087
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.01
2.45
1.07
12.10
3.10
2.22


OH
H
S*
R*
S*
S*
Me
OH

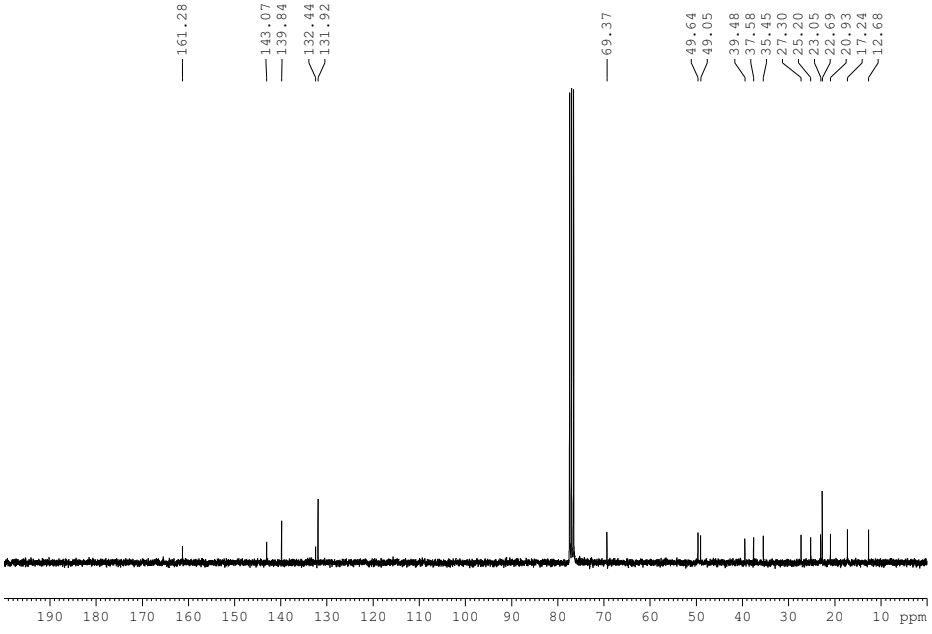
194

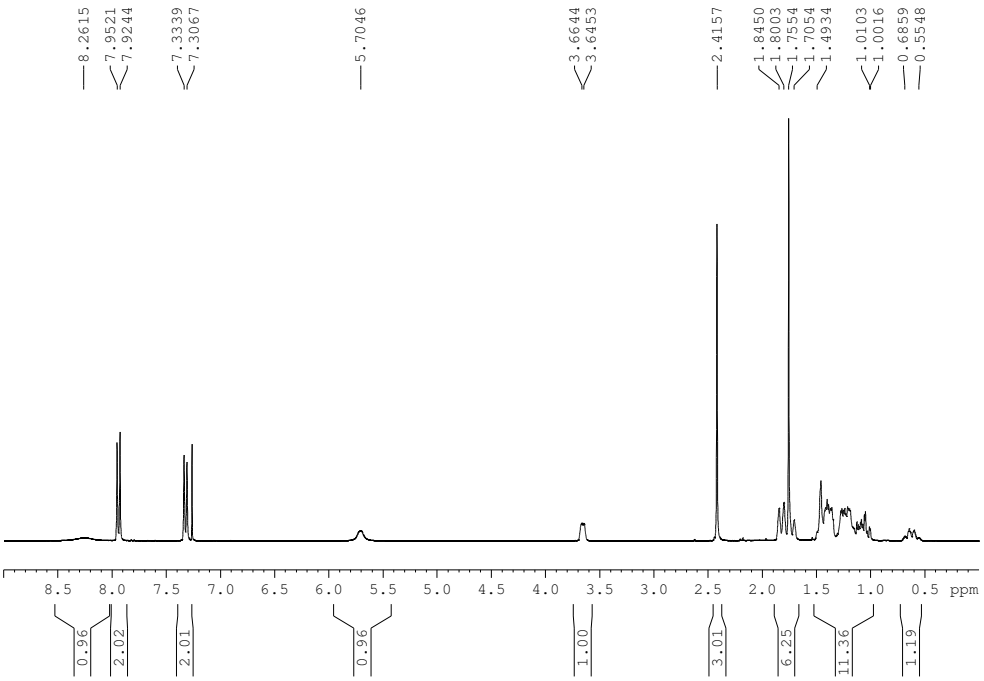

72.21
71.86
50.76
39.19
38.38
37.61
34.62
28.57
27.49
22.99
18.49
17.29
130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

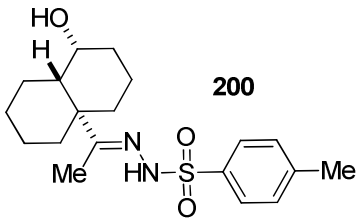

6.9689
5.3323
3.5993
2.6923
2.2858
1.8352
1.7907
1.7574
1.4348
0.9918
0.6525
0.5209
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.08
1.04
1.07
6.05
3.12
6.07
12.20
1.24


HO
H
Me
N
Me
HN
S
O
O
Me
Me
Me

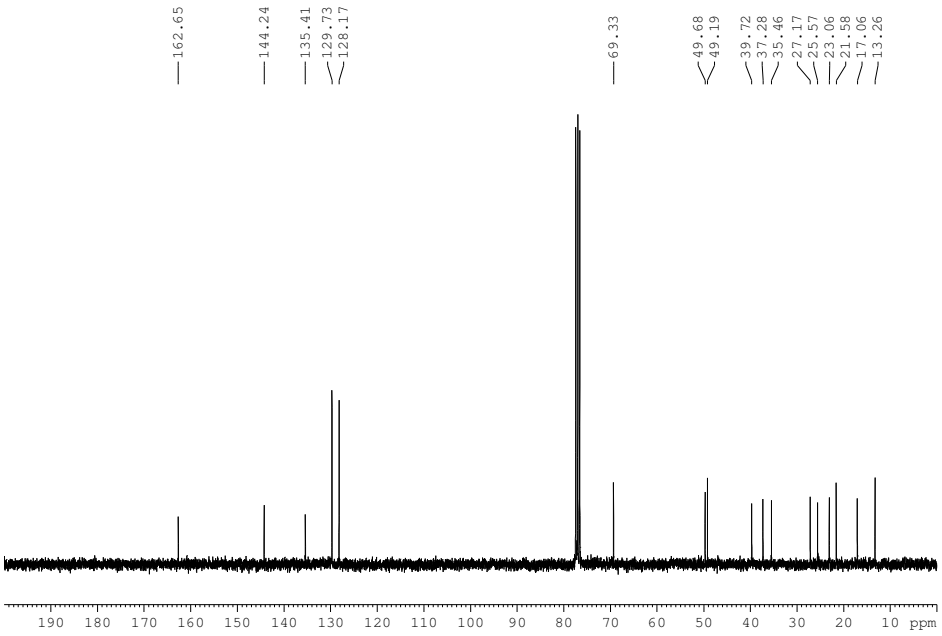
199

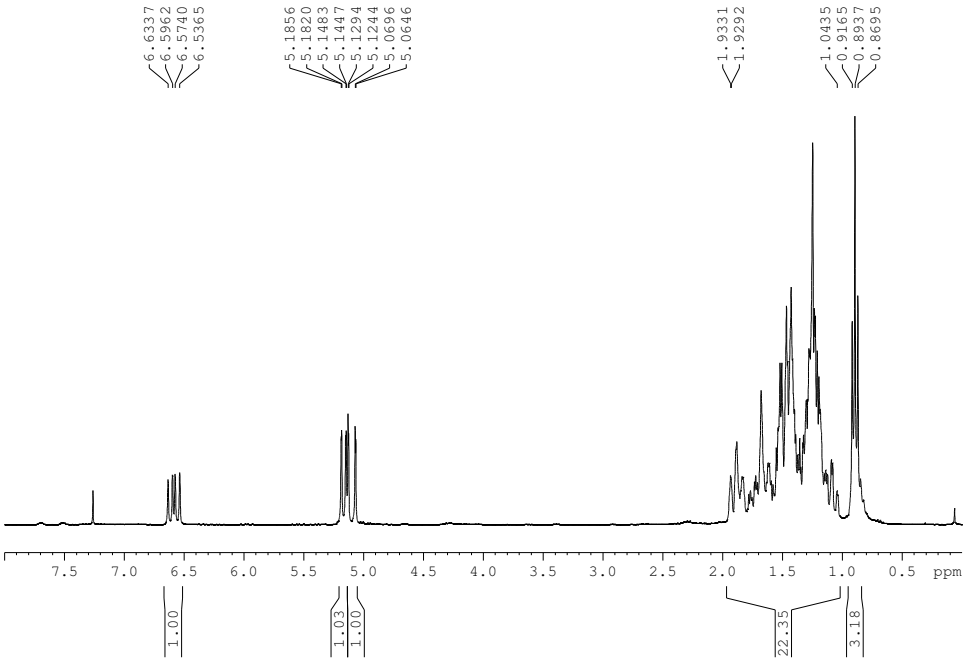

161.28
143.07
139.84
132.44
131.92
69.37
49.64
49.05
39.48
37.58
35.45
27.30
25.20
23.05
22.69
20.93
17.24
12.68
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

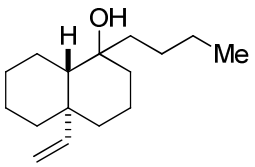

8.2615
7.9521
7.9244
7.3339
7.3067
5.7046
3.6644
3.6453
2.4157
1.8450
1.8003
1.7554
1.7054
1.4934
1.0103
1.0016
0.6859
0.5548
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.96
2.02
2.01
0.96
1.00
3.01
6.25
11.36
1.19


HO
H
N
Me
HN
S
O
O
Me

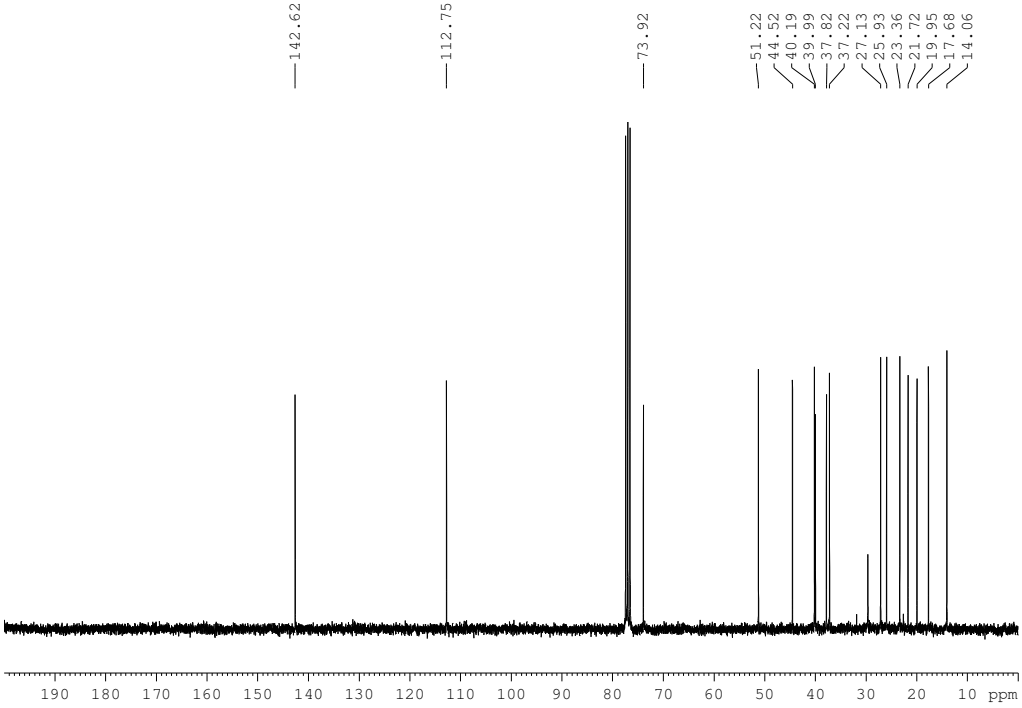
200

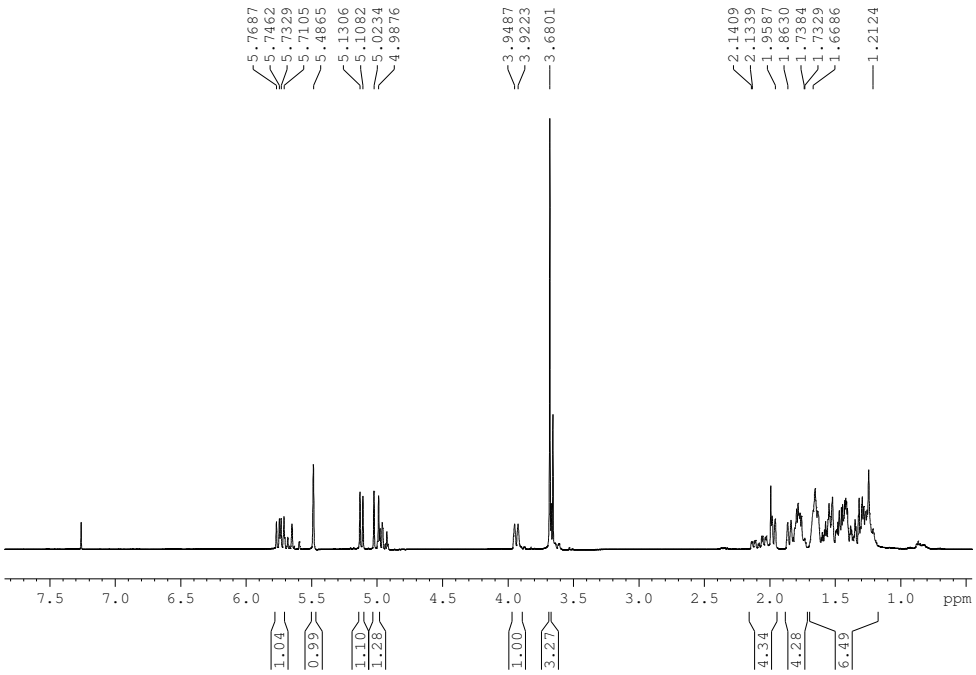

162.65
144.24
135.41
129.73
128.17
69.33
49.68
49.19
39.72
37.28
35.46
27.17
25.57
23.06
21.58
17.06
13.26
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

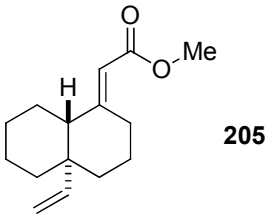

6.6337
6.5962
6.5740
6.5365
5.1856
5.1820
5.1483
5.1447
5.1294
5.1244
5.0696
5.0646
1.9331
1.9292
1.0435
0.9165
0.8937
0.8695
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.03
1.00
22.35
3.18


OH
H
Me

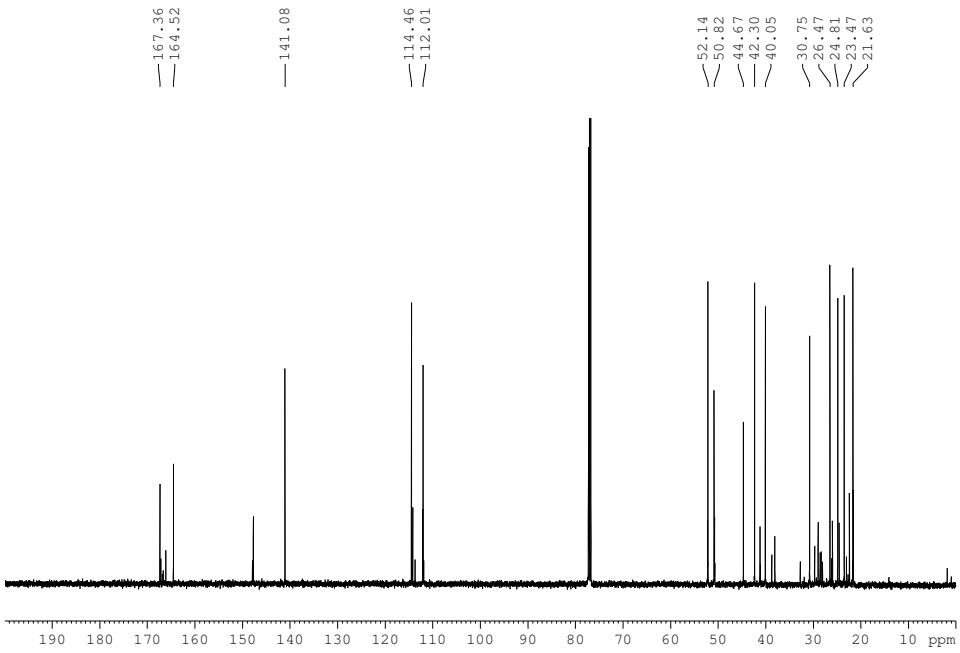
203

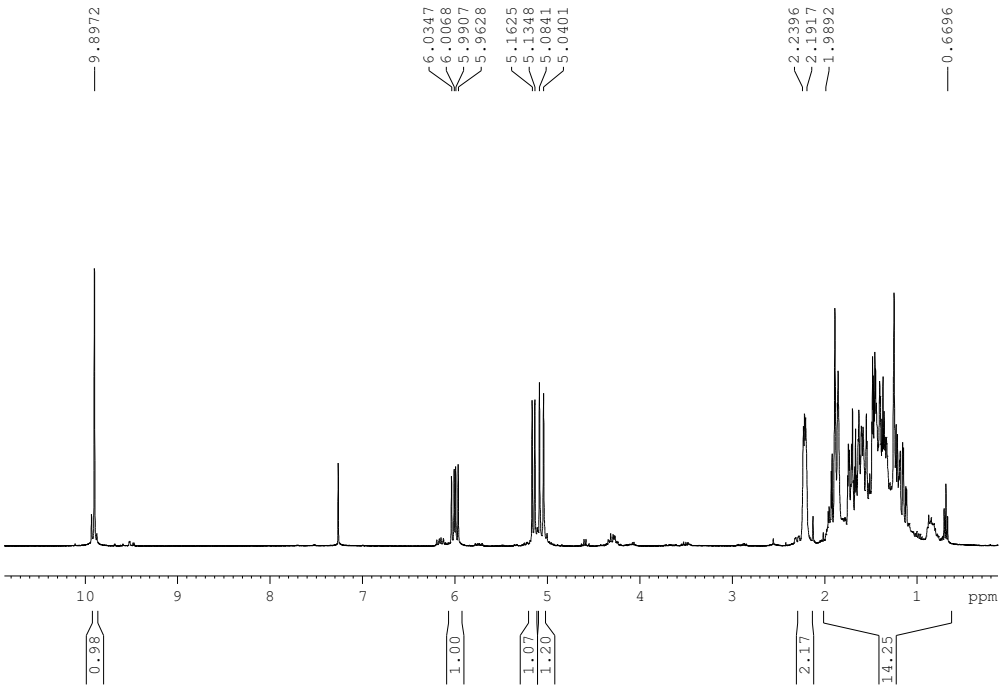

142.62
112.75
73.92
51.22
44.52
40.19
39.99
37.82
37.22
27.13
25.93
23.36
21.72
19.95
17.68
14.06
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

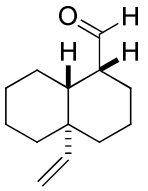

5.7687
5.7462
5.7329
5.7105
5.4865
5.1306
5.1082
5.0234
4.9876
3.9487
3.9223
3.6801
2.1409
2.1339
1.9587
1.8630
1.7384
1.7329
1.6686
1.2124
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.04
0.99
1.10
1.28
1.00
3.27
4.34
4.28
6.49


O
O
Me
H

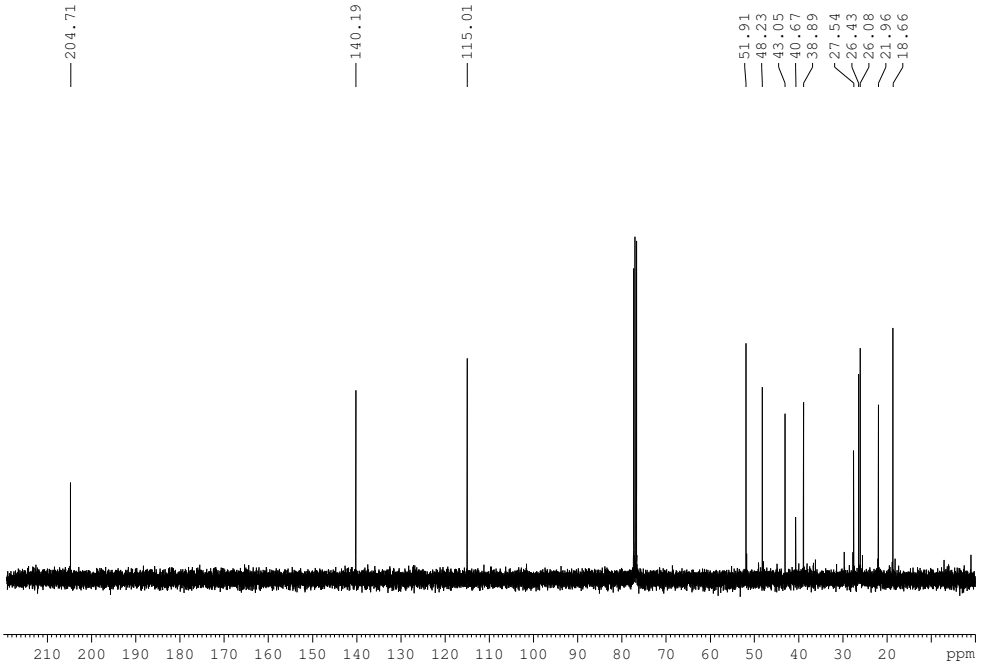
205

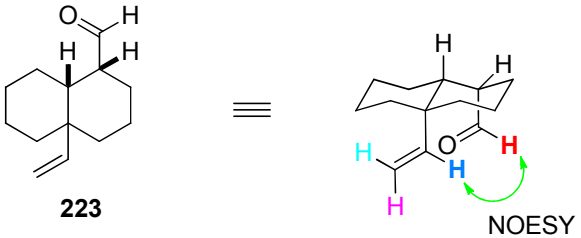

167.36
164.52
141.08
114.46
112.01
52.14
50.82
44.67
42.30
40.05
30.75
26.47
24.81
23.47
21.63
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

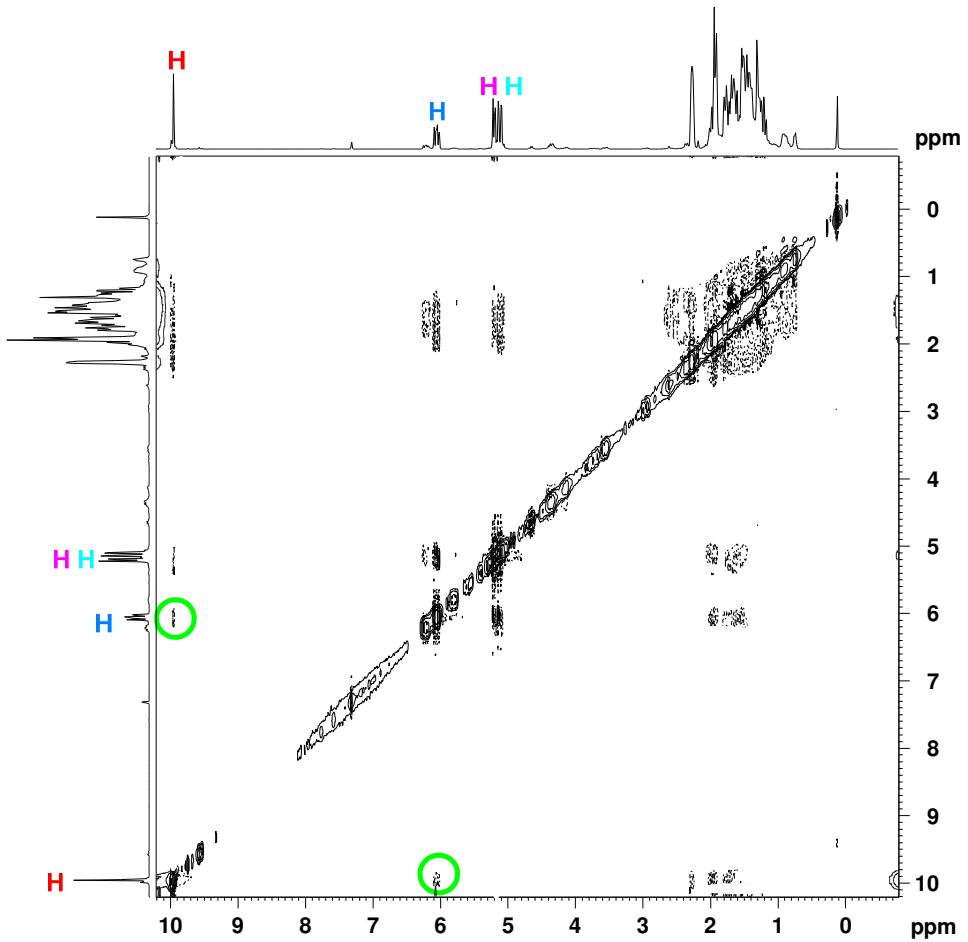

9.8972
6.0347
6.0068
5.9907
5.9628
5.1625
5.1348
5.0841
5.0401
2.2396
2.1917
1.9892
0.6696
10
9
8
7
6
5
4
3
2
1
ppm
0.98
1.00
1.07
1.20
2.17
14.25

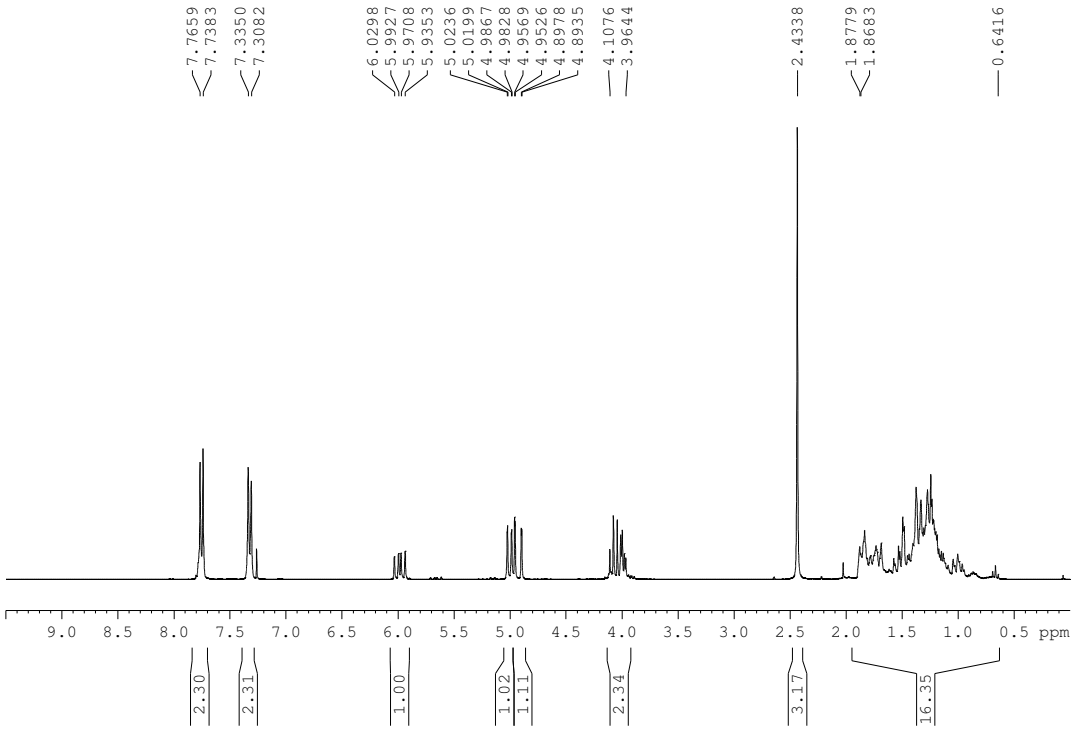


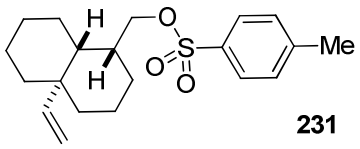
223


204.71
140.19
115.01
51.91
48.23
43.05
40.67
38.89
27.54
26.43
26.08
21.96
18.66
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

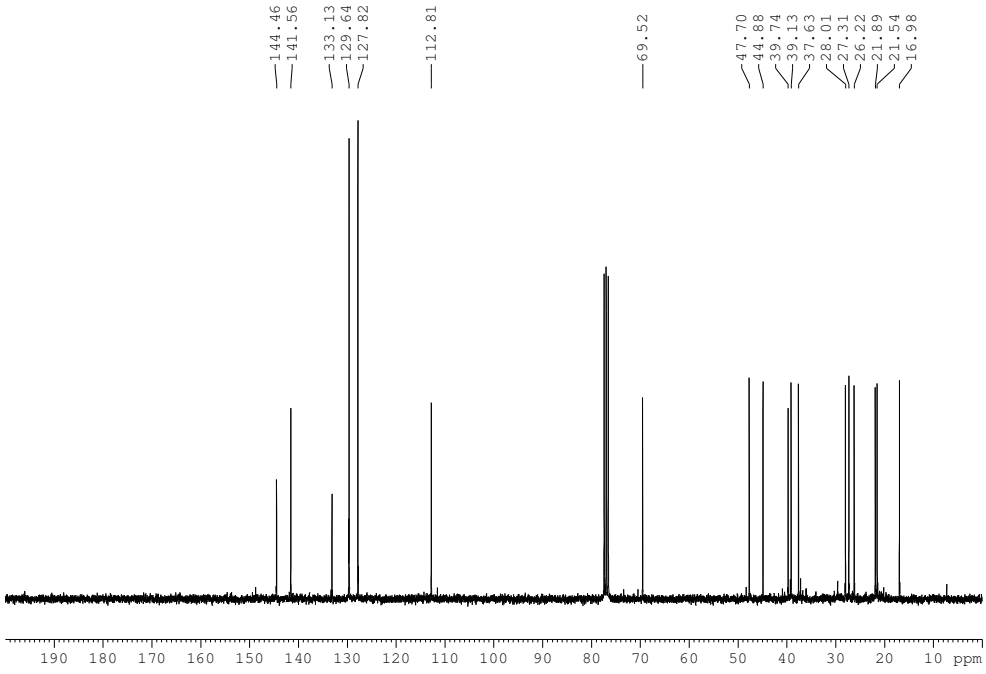

O
H
H
H
223
NOESY

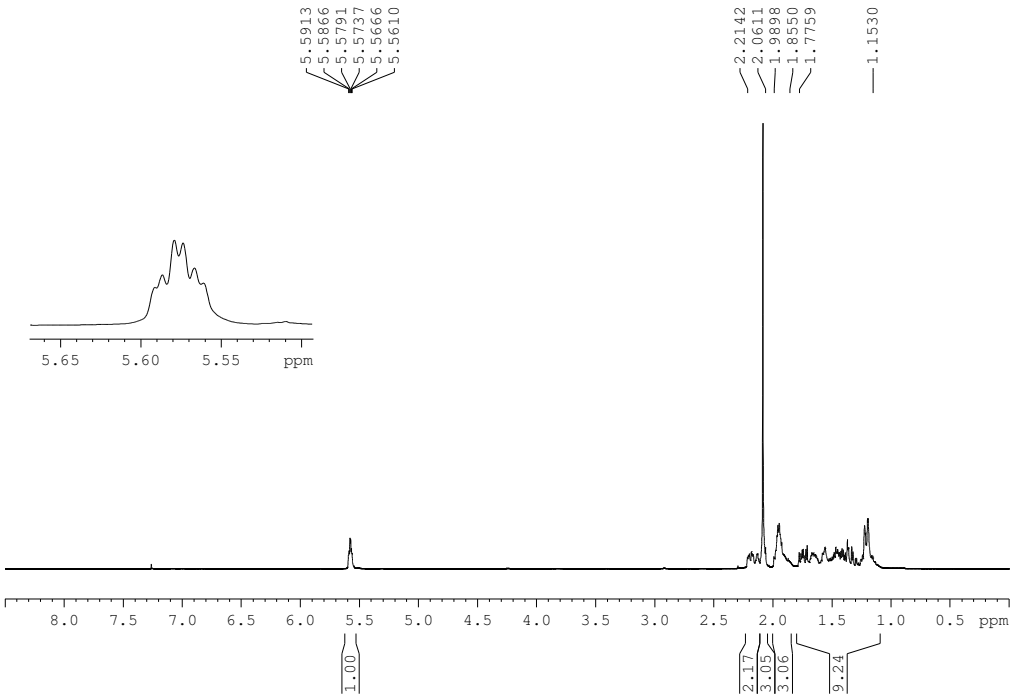

H
H
H H
H H
H
H
ppm
0
1
2
3
4
5
6
7
8
9
10
10 9 8 7 6 5 4 3 2 1 0
ppm

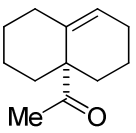

7.7659
7.7383
7.3350
7.3082
6.0298
5.9927
5.9708
5.9353
5.0236
5.0199
4.9867
4.9828
4.9569
4.9526
4.8978
4.8935
4.1076
3.9644
2.4338
1.8779
1.8683
0.6416
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.30
2.31
1.00
1.02
1.11
2.34
3.17
16.35


H
O
S
O
O
H
Me

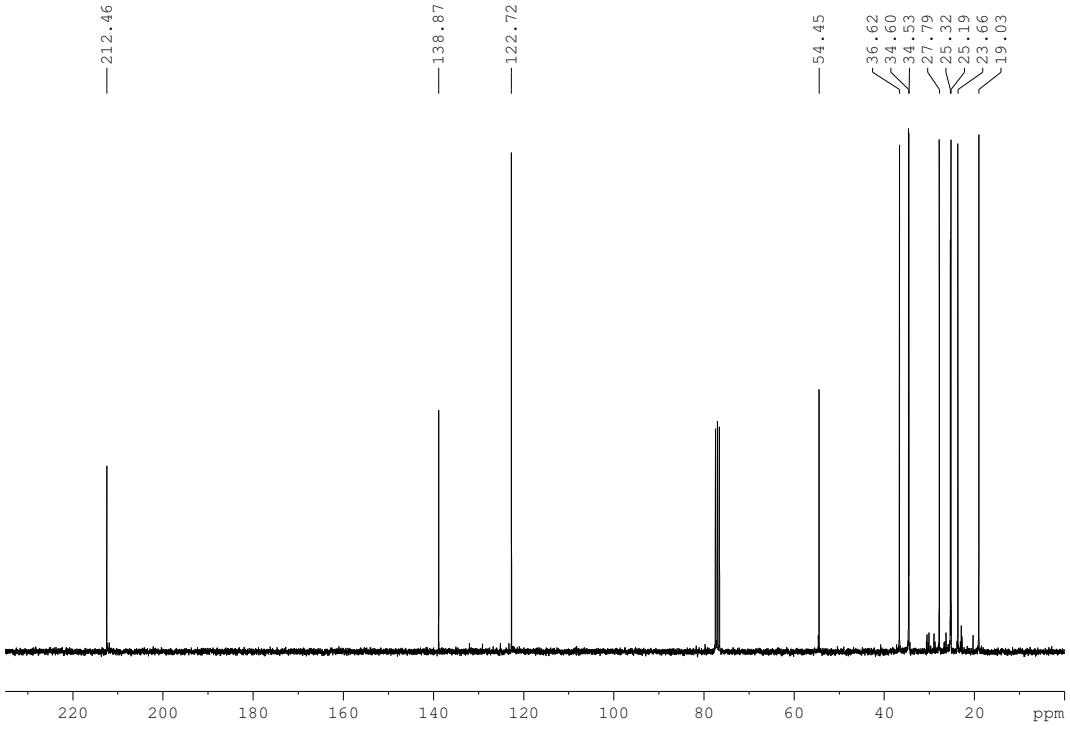
231

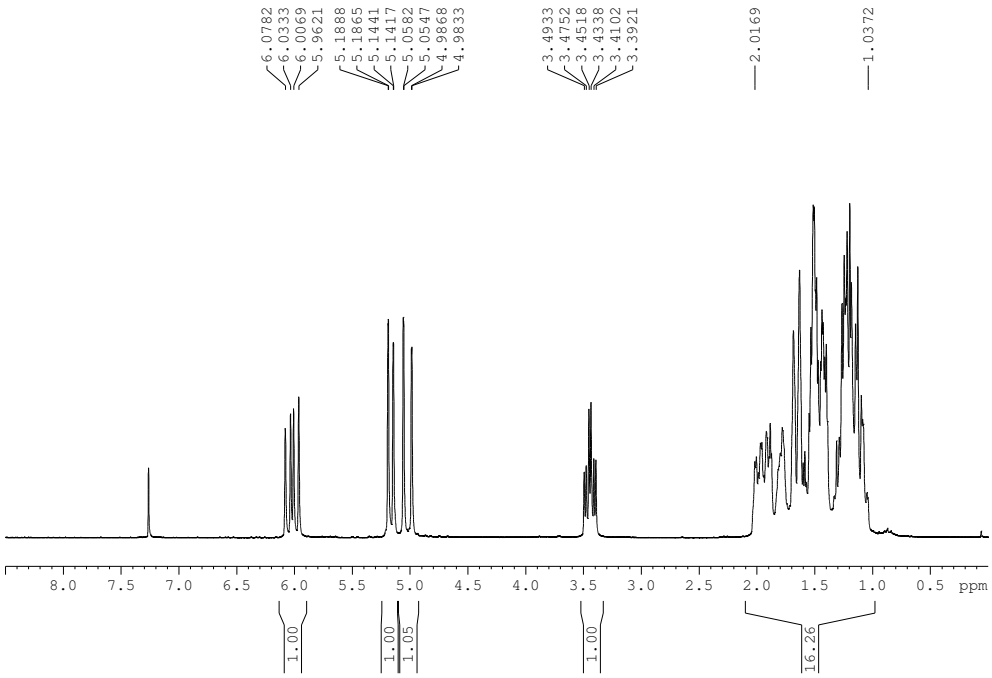

144.46
141.56
133.13
129.64
127.82
112.81
69.52
47.70
44.88
39.74
39.13
37.63
28.01
27.31
26.22
21.89
21.54
16.98
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

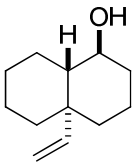

5.5913
5.5866
5.5791
5.5737
5.5666
5.5610
2.2142
2.0611
1.9898
1.8550
1.7759
1.1530
5.65
5.60
5.55
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.17
3.05
3.06
9.24


Me
O

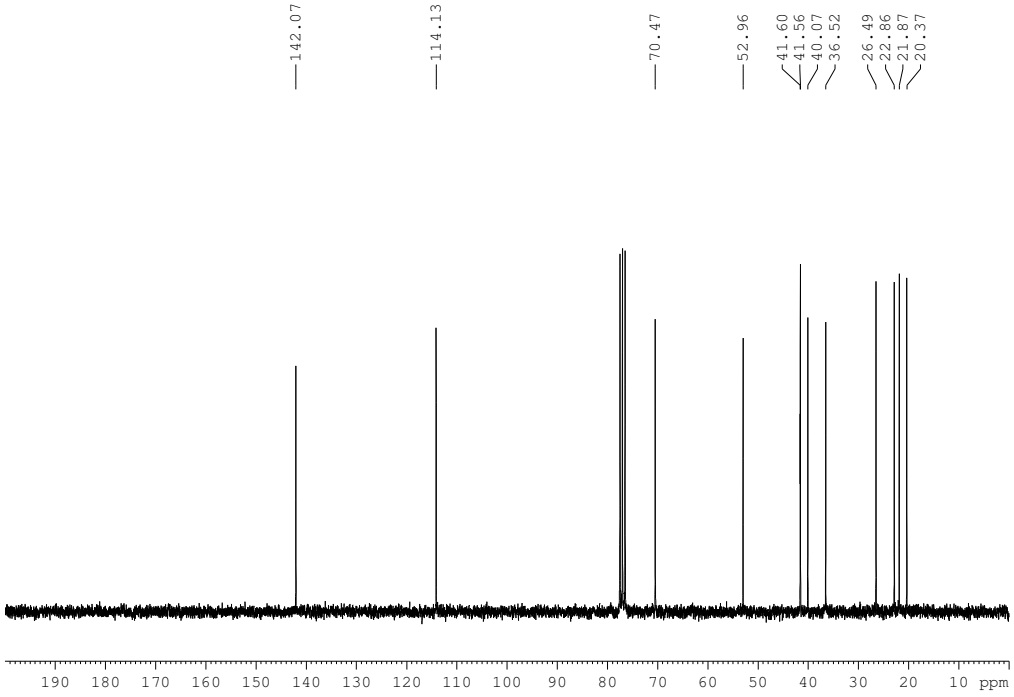
232

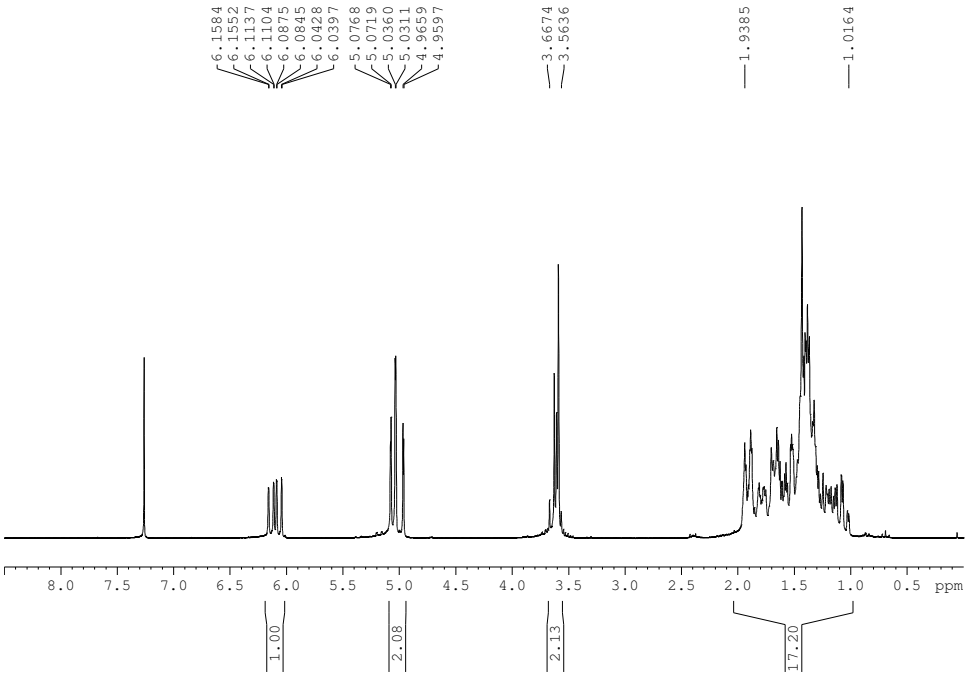

212.46
138.87
122.72
54.45
36.62
34.60
34.53
27.79
25.32
25.19
23.66
19.03
220
200
180
160
140
120
100
80
60
40
20
ppm

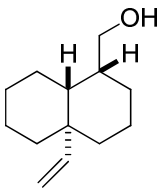

6.0782
6.0333
6.0069
5.9621
5.1888
5.1865
5.1441
5.1417
5.0582
5.0547
4.9868
4.9833
3.4933
3.4752
3.4518
3.4338
3.4102
3.3921
2.0169
1.0372
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.00
1.05
1.00
16.26


H
OH

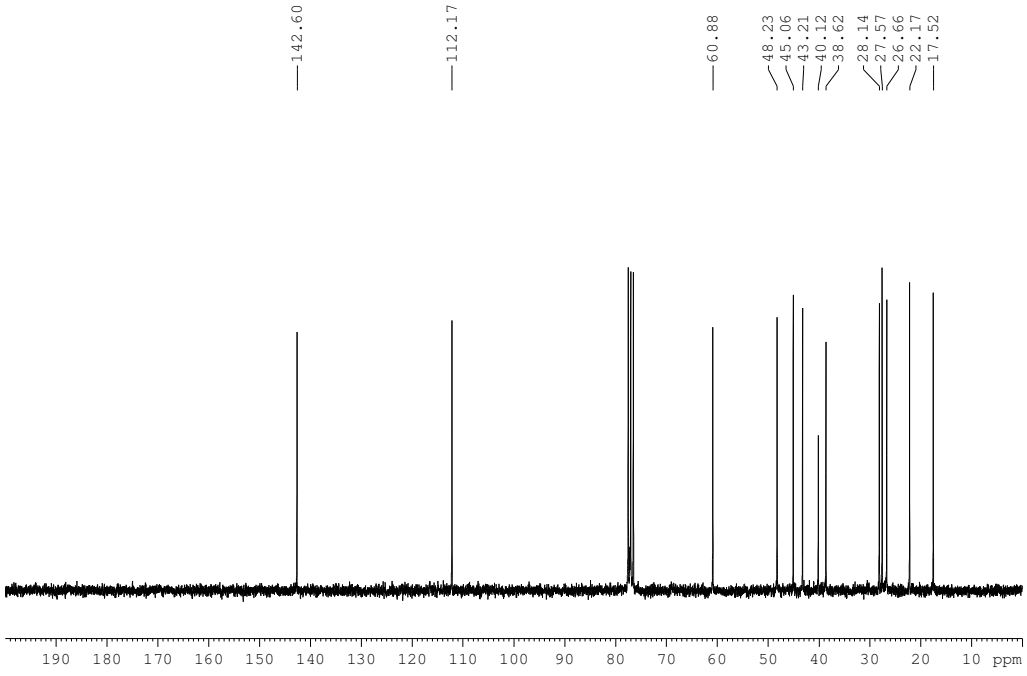
248

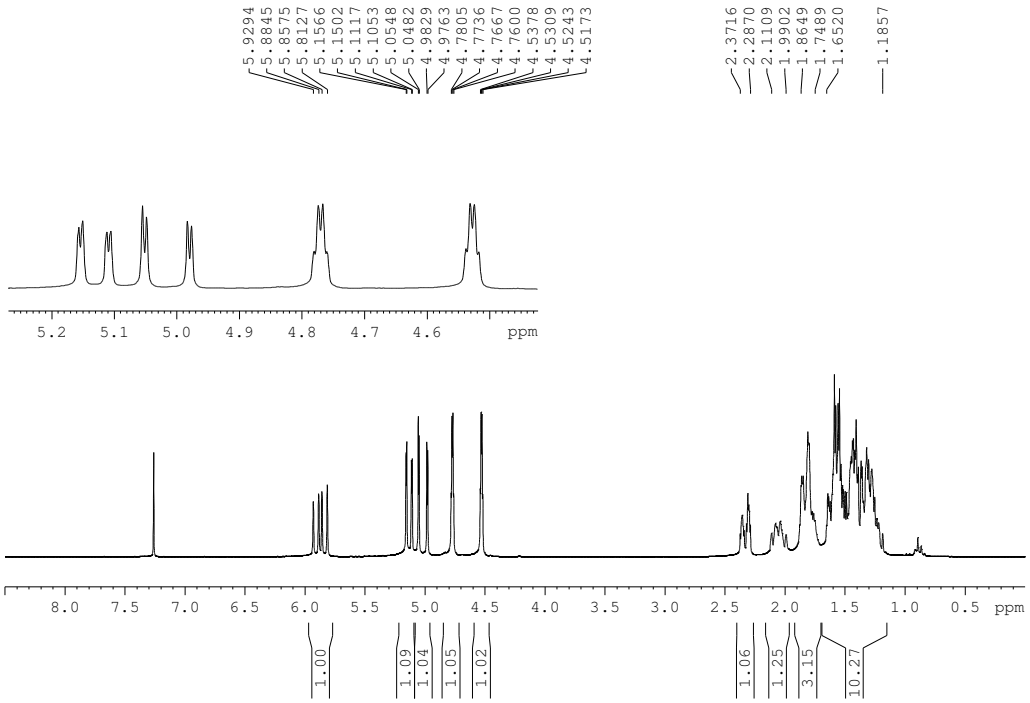

142.07
114.13
70.47
52.96
41.60
41.56
40.07
36.52
26.49
22.86
21.87
20.37
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

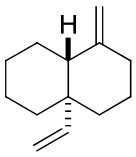

6.1584
6.1552
6.1137
6.1104
6.0875
6.0845
6.0428
6.0397
5.0768
5.0719
5.0360
5.0311
4.9659
4.9597
3.6674
3.5636
1.9385
1.0164
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.08
2.13
17.20


OH
H
H

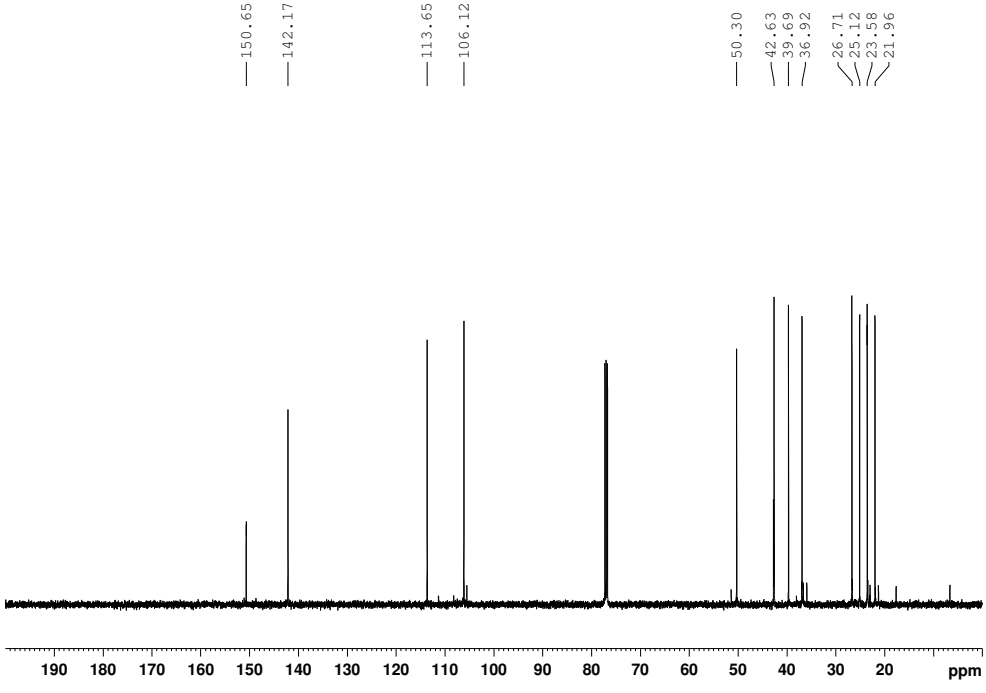
249

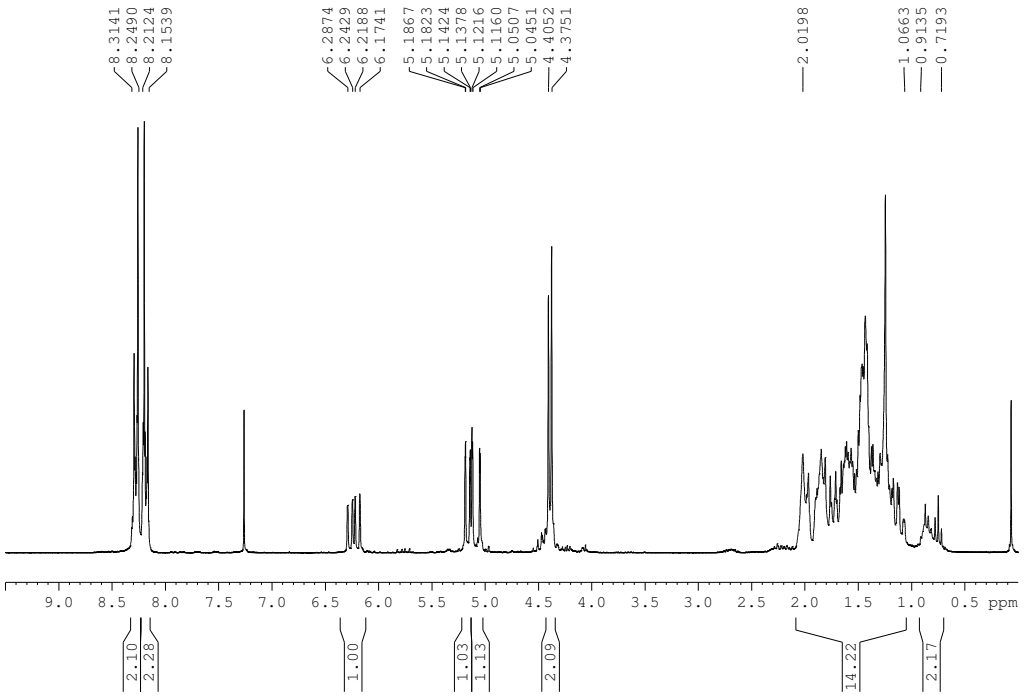

142.60
112.17
60.88
48.23
45.06
43.21
40.12
38.62
28.14
27.57
26.66
22.17
17.52
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

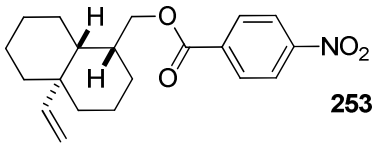

5.9294
5.8845
5.8575
5.8127
5.1566
5.1502
5.1117
5.1053
5.0548
5.0482
4.9829
4.9763
4.7805
4.7736
4.7667
4.7600
4.5378
4.5309
4.5243
4.5173
2.3716
2.2870
2.1109
1.9902
1.8649
1.7489
1.6520
1.1857
5.2 5.1 5.0 4.9 4.8 4.7 4.6 ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.09
1.04
1.05
1.02
1.06
1.25
3.15
10.27


H

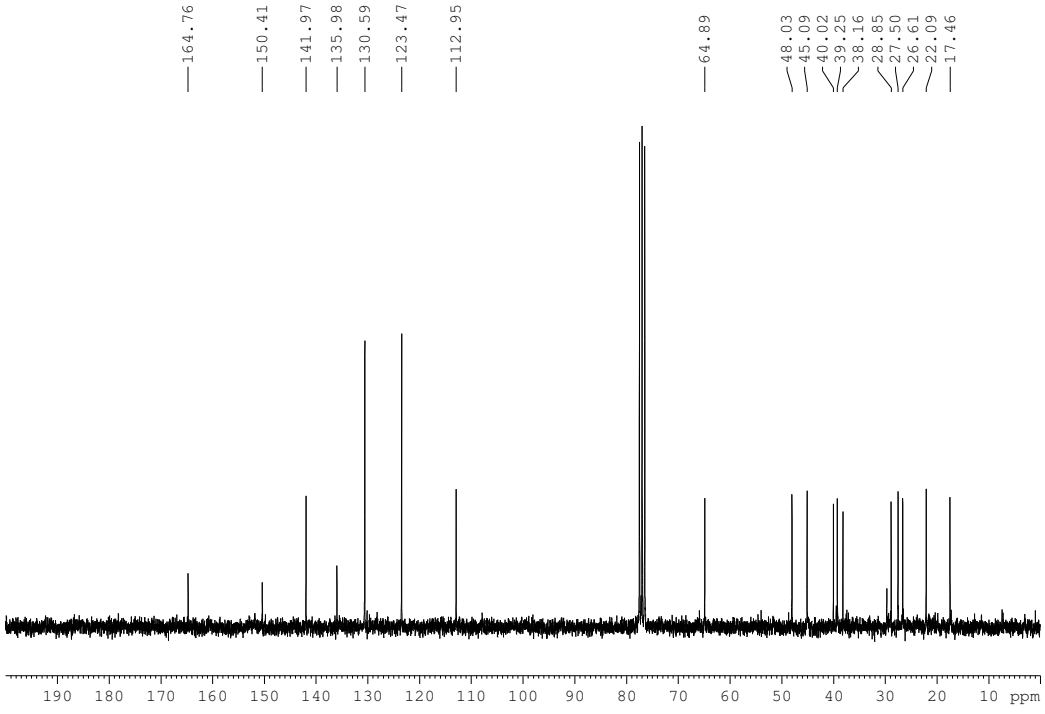
250

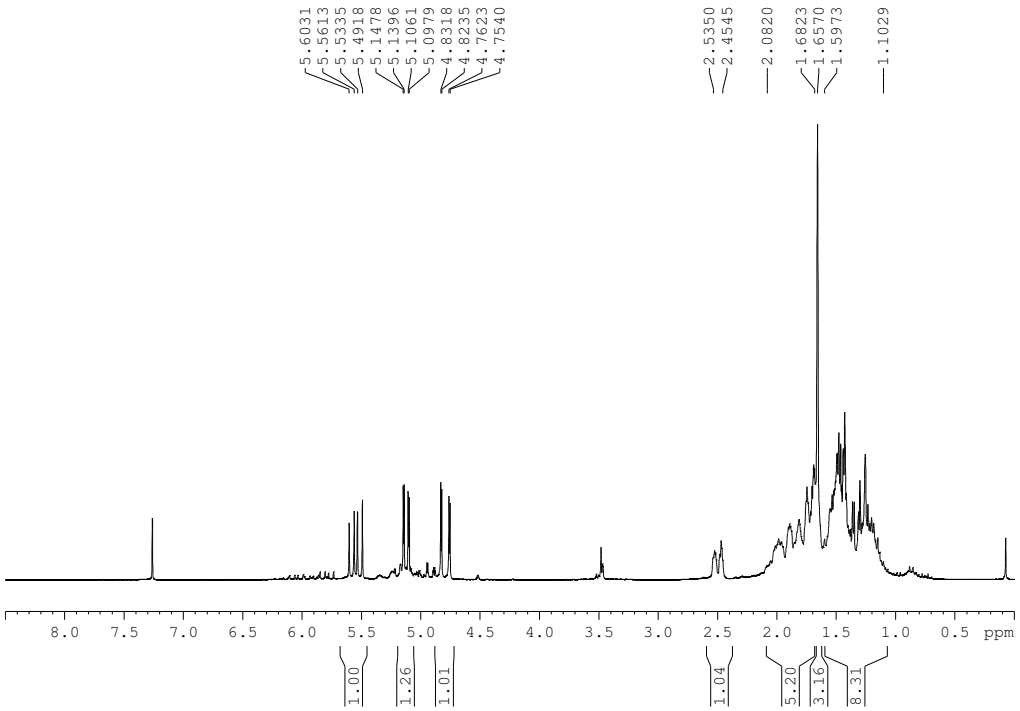

150.65
142.17
113.65
106.12
50.30
42.63
39.69
36.92
26.71
25.12
23.58
21.96
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

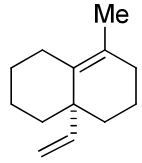

8.3141
8.2490
8.2124
8.1539
6.2874
6.2429
6.2188
6.1741
5.1867
5.1823
5.1424
5.1378
5.1216
5.1160
5.0507
5.0451
4.4052
4.3751
2.0198
1.0663
0.9135
0.7193
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.10
2.28
1.00
1.03
1.13
2.09
14.22
2.17


H
O
NO2
H
O

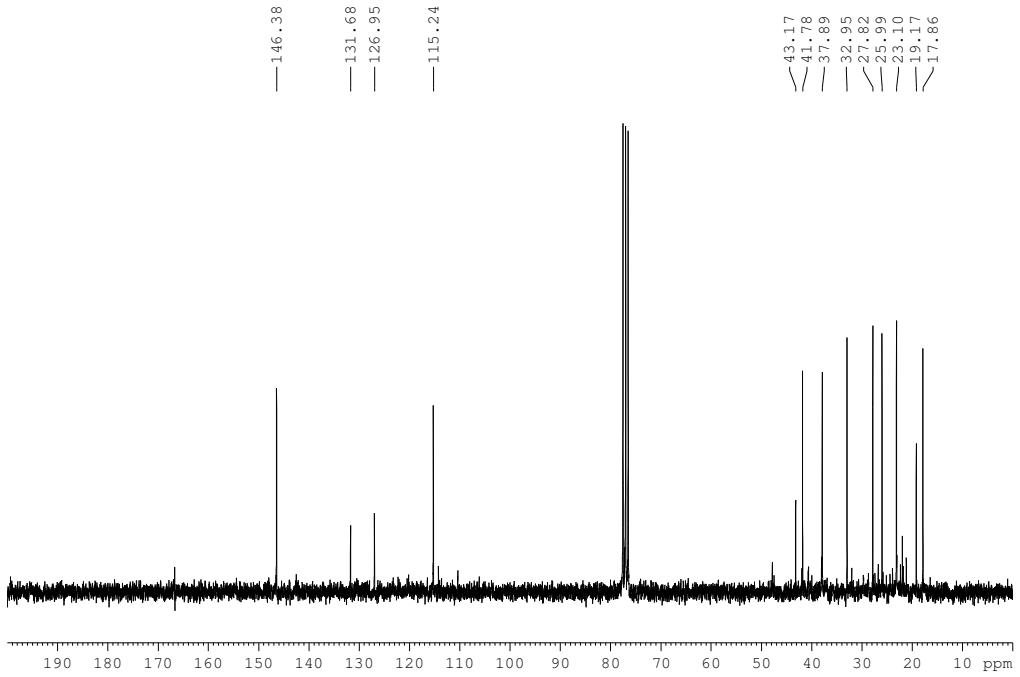
253

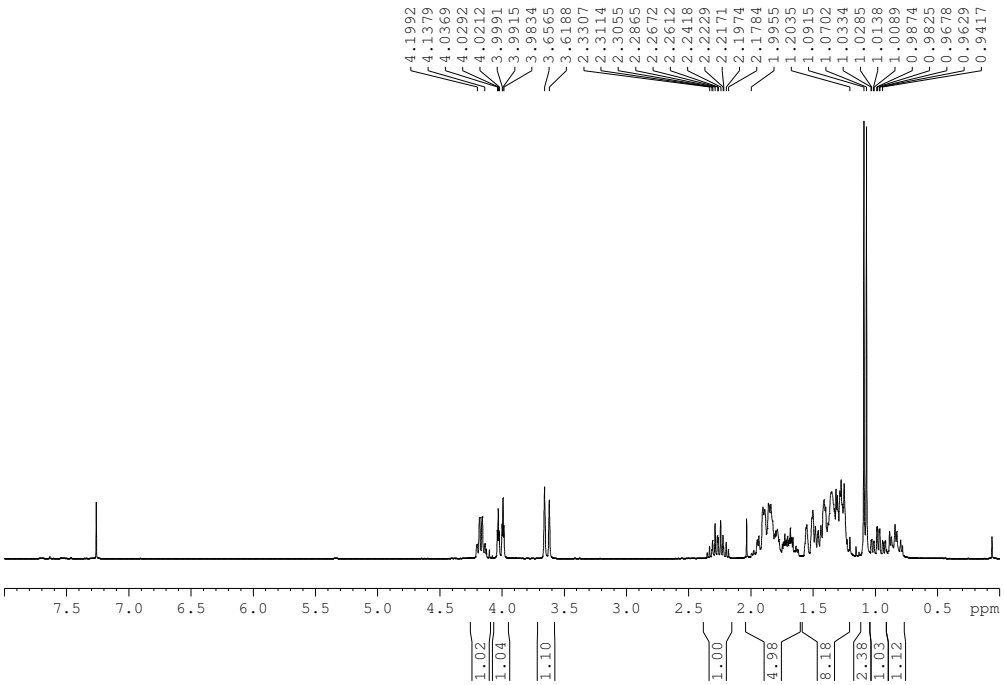

164.76
150.41
141.97
135.98
130.59
123.47
112.95
64.89
48.03
45.09
40.02
39.25
38.16
28.85
27.50
26.61
22.09
17.46
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

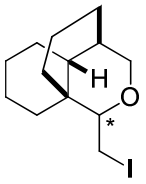

5.6031
5.5613
5.5335
5.4918
5.1478
5.1396
5.1061
5.0979
4.8318
4.8235
4.7623
4.7540
2.5350
2.4545
2.0820
1.6823
1.6570
1.5973
1.1029
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.26
1.01
1.04
5.20
3.16
8.31


Me

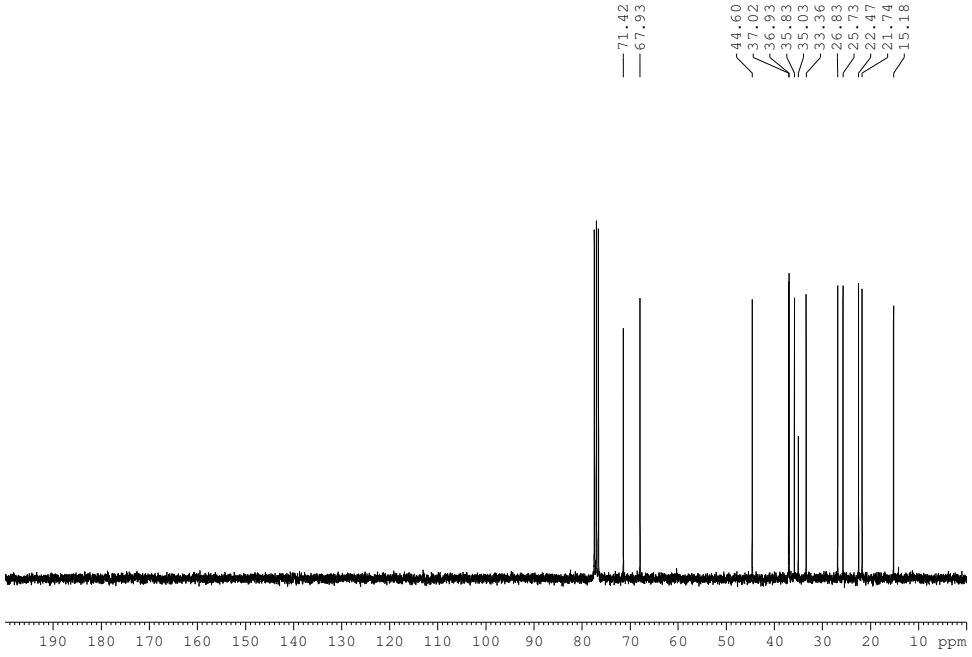
261

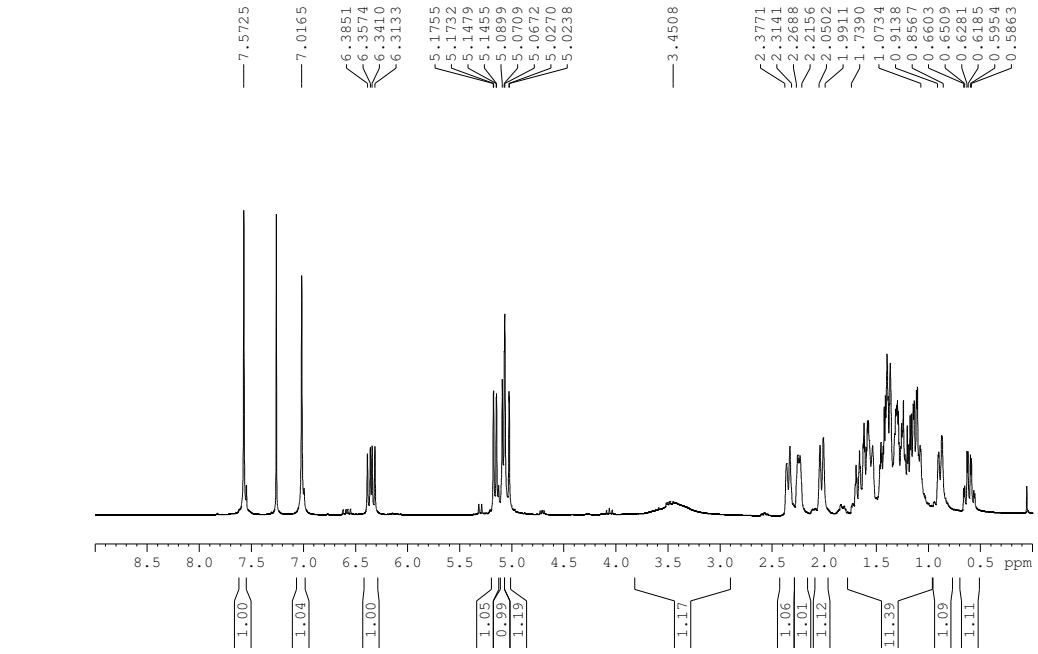

146.38
131.68
126.95
115.24
43.17
41.78
37.89
32.95
27.82
25.99
23.10
19.17
17.86
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

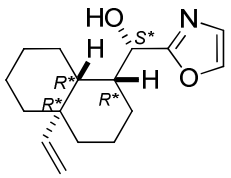

4.1992
4.1379
4.0369
4.0292
4.0212
3.9991
3.9915
3.9834
3.6565
3.6188
2.3307
2.3114
2.3055
2.2865
2.2672
2.2612
2.2418
2.2229
2.2171
2.1974
2.1784
1.9955
1.2035
1.0915
1.0702
1.0334
1.0285
1.0138
1.0089
0.9874
0.9825
0.9678
0.9629
0.9417
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.02
1.04
1.10
1.00
4.98
8.18
2.38
1.03
1.12


H
O
*
I

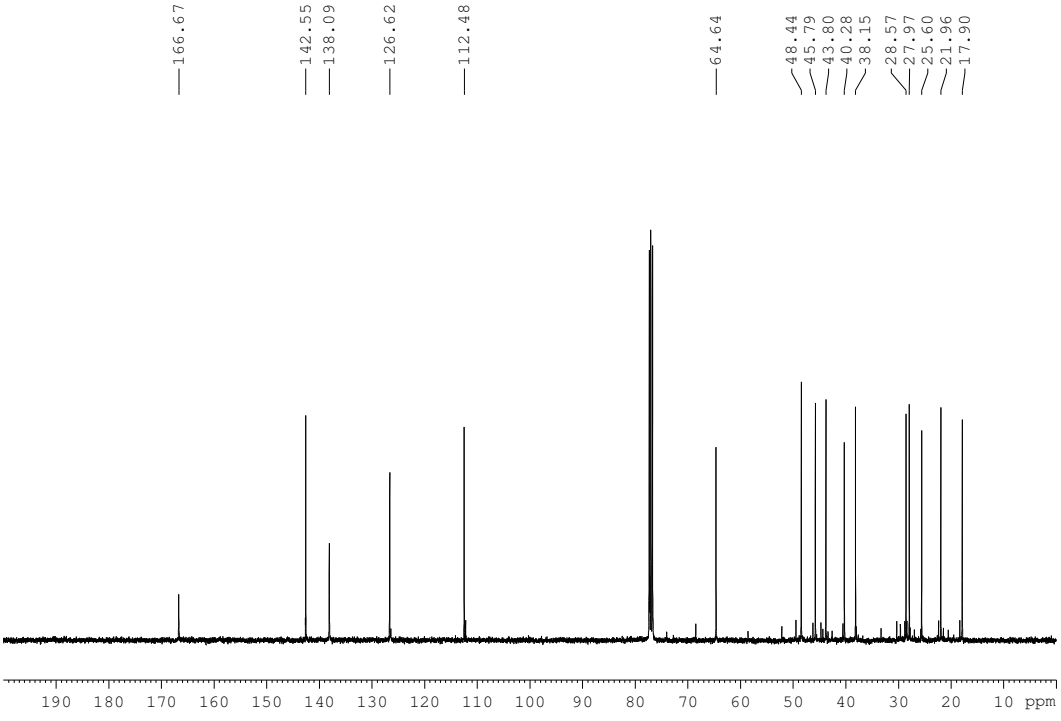
262

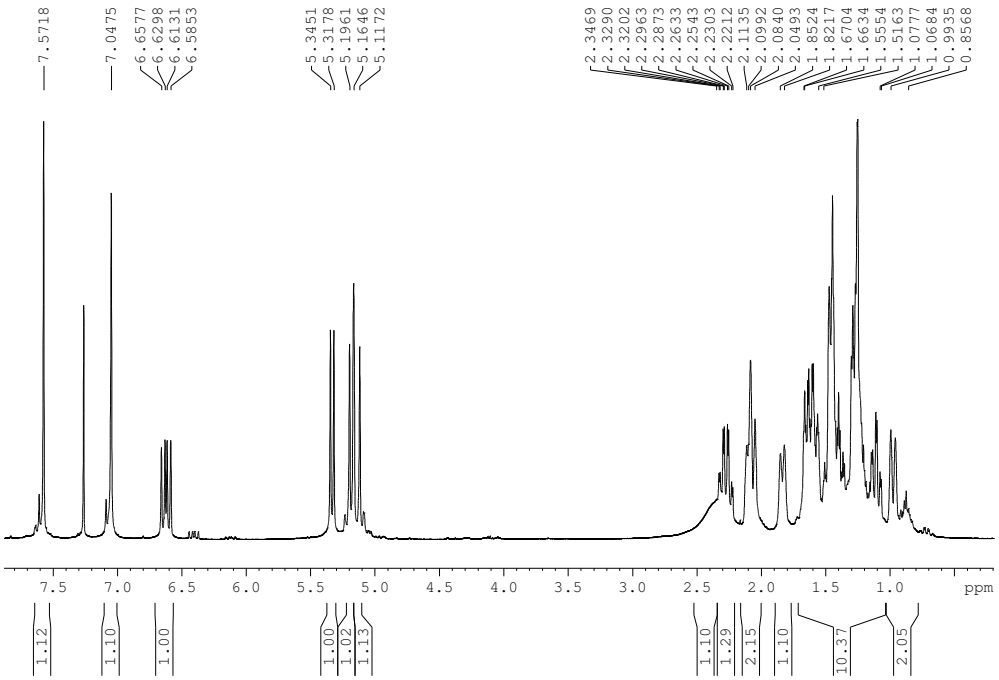

71.42
67.93
44.60
37.02
36.93
35.83
35.03
33.36
26.83
25.73
22.47
21.74
15.18
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

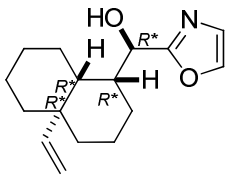

7.5725
7.0165
6.3851
6.3574
6.3410
6.3133
5.1755
5.1732
5.1479
5.1455
5.0899
5.0709
5.0672
5.0270
5.0238
3.4508
2.3771
2.3141
2.2688
2.2156
2.0502
1.9911
1.7390
1.0734
0.9138
0.8567
0.6603
0.6509
0.6281
0.6185
0.5954
0.5863
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.04
1.00
1.05
0.99
1.19
1.17
1.06
1.01
1.12
11.39
1.09
1.11


HO
S*
N
H
R*
H
O
R*
R*

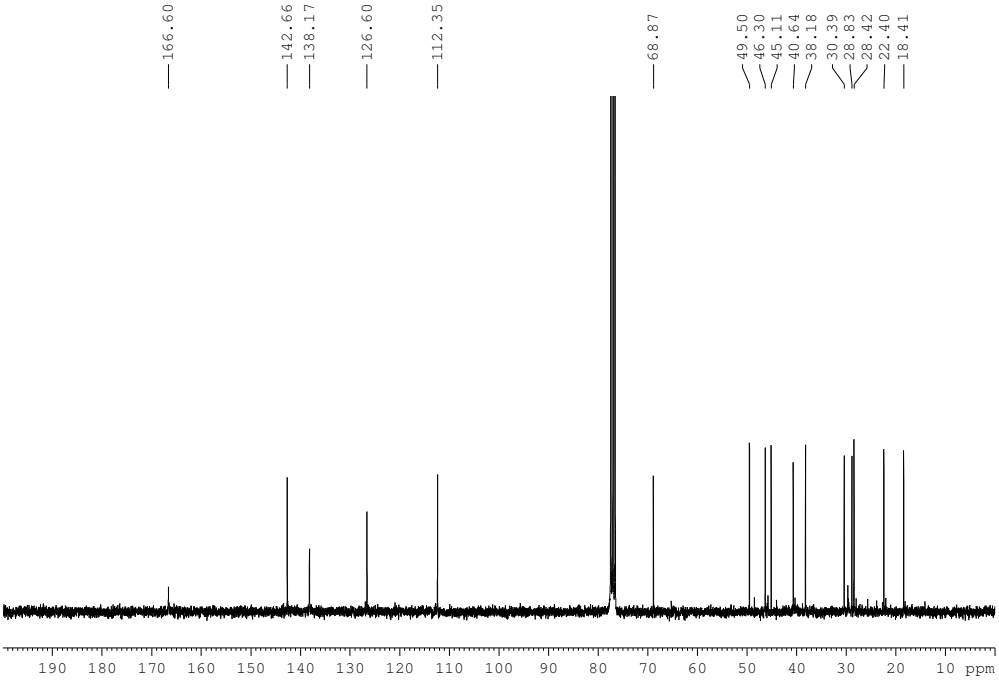
266

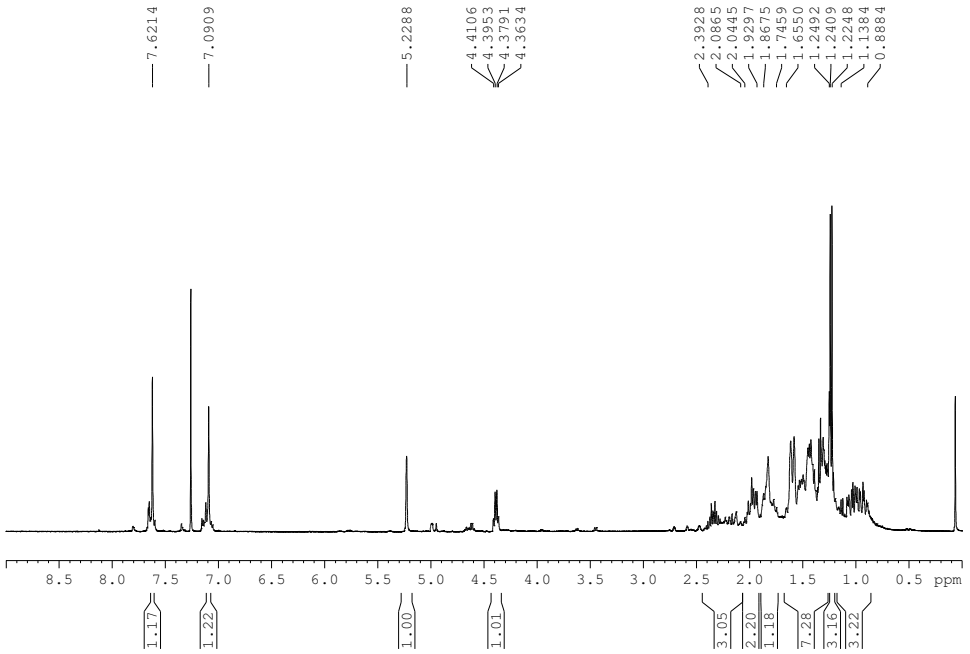

166.67
142.55
138.09
126.62
112.48
64.64
48.44
45.79
43.80
40.28
38.15
28.57
27.97
25.60
21.96
17.90
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

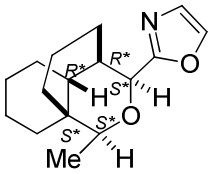

7.5718
7.0475
6.6577
6.6298
6.6131
6.5853
5.3451
5.3178
5.1961
5.1646
5.1172
2.3469
2.3290
2.3202
2.2963
2.2873
2.2633
2.2543
2.2303
2.2212
2.1135
2.0992
2.0840
2.0493
1.8524
1.8217
1.6704
1.6634
1.5554
1.5163
1.0777
1.0684
0.9935
0.8568
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.12
1.10
1.00
1.00
1.02
1.13
1.10
1.29
2.15
1.10
10.37
2.05


HO
N
H
R*
H
O
R*
R*
R*

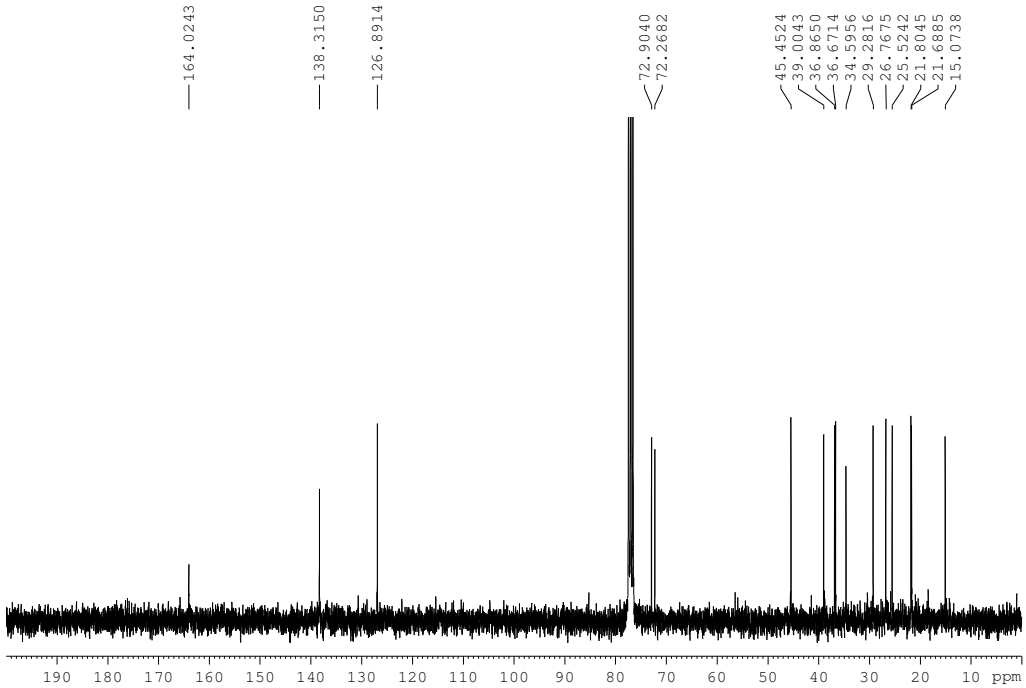
267

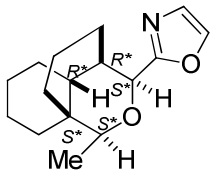

166.60
142.66
138.17
126.60
112.35
68.87
49.50
46.30
45.11
40.64
38.18
30.39
28.83
28.42
22.40
18.41
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.6214
7.0909
5.2288
4.4106
4.3953
4.3791
4.3634
2.3928
2.0865
2.0445
1.9297
1.8675
1.7459
1.6550
1.2492
1.2409
1.2248
1.1384
0.8884
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.17
1.22
1.00
1.01
3.05
2.20
1.18
7.28
3.16
3.22


N
O
R*
R*
H
S*
H
O
S*
S*
Me
H

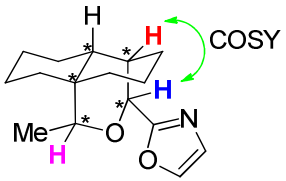
269

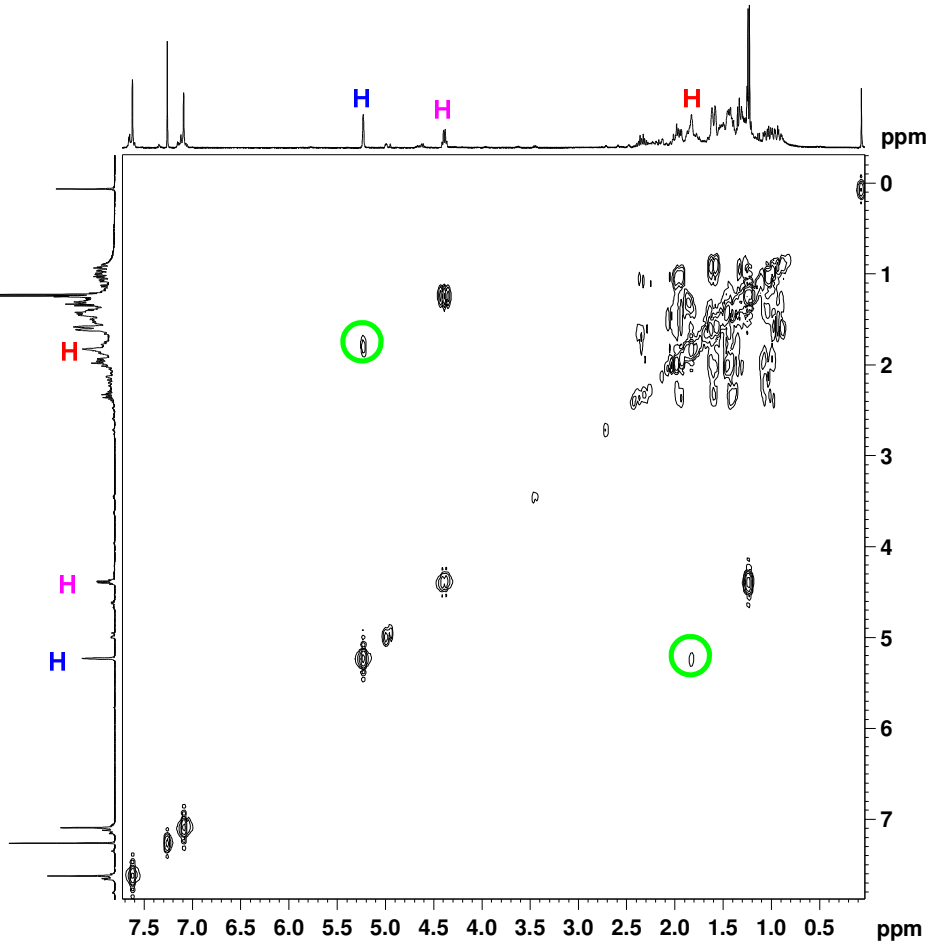

164.0243
138.3150
126.8914
72.9040
72.2682
45.4524
39.0043
36.8650
36.6714
34.5956
29.2816
26.7675
25.5242
21.8045
21.6885
15.0738
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

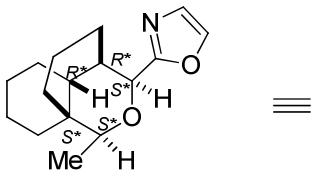

N
O
R*
R*
H
S*
H
S*
O
S*
Me
H

269

≡

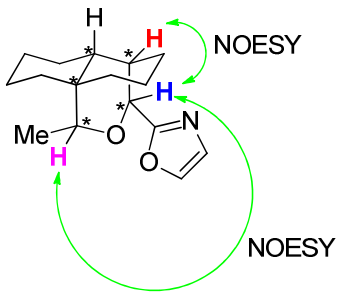

H
H
COSY
H
Me
H
O
N
O

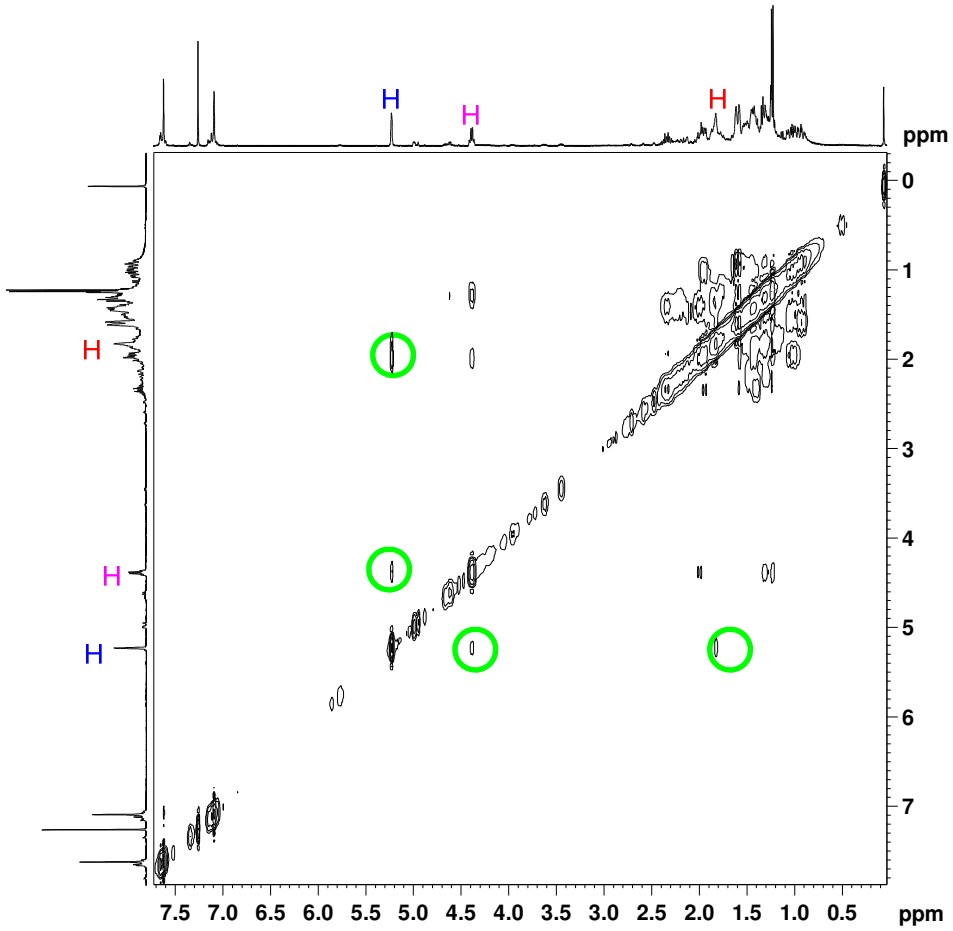

H
H
H
ppm
H
H
H
0
1
2
3
4
5
6
7
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

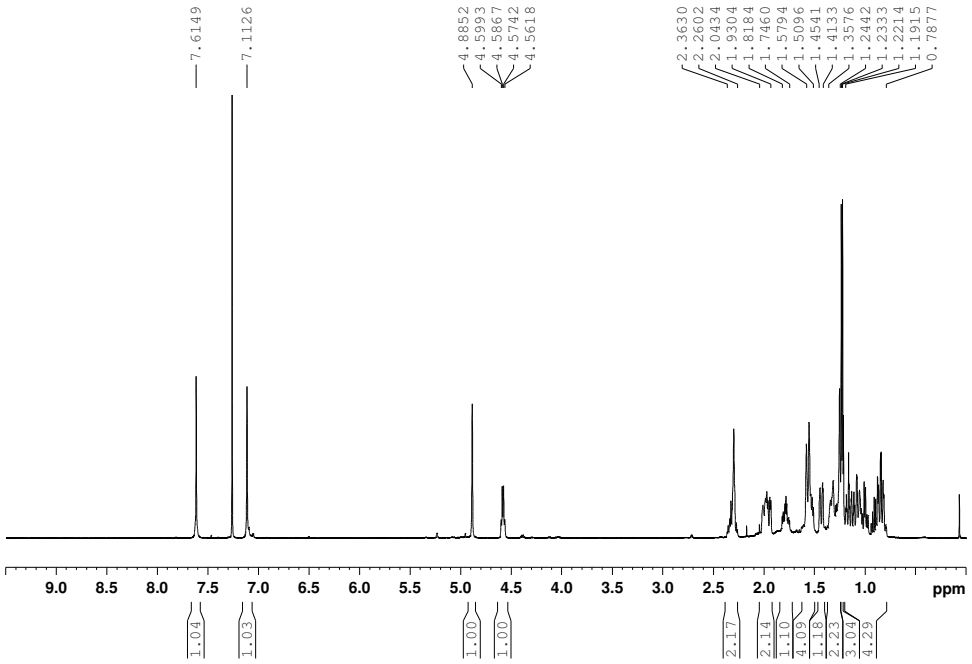

N
O
R*
R*
H
S*
H
O
S*
S*
Me
H

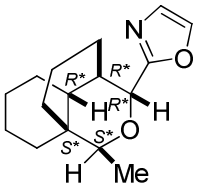
269

≡

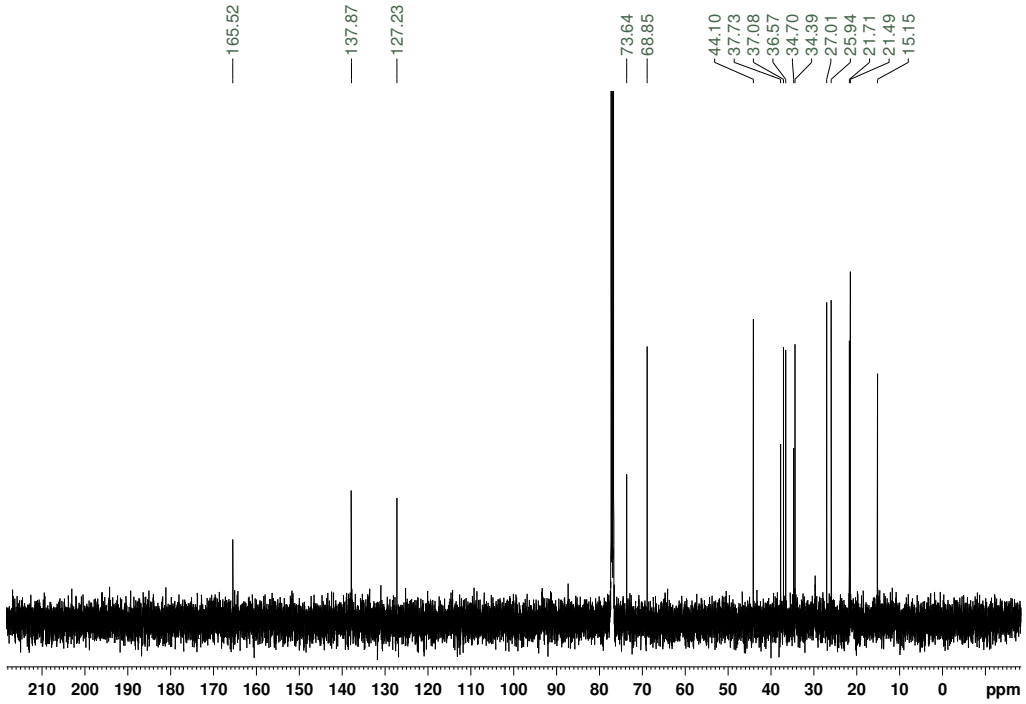

H
H
NOESY
H
Me
O
N
O
H
NOESY

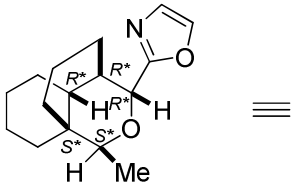

H
H
H
ppm
H
H
H
0
1
2
3
4
5
6
7
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm


7.6149
7.1126
4.8852
4.5993
4.5867
4.5742
4.5618
2.3630
2.2602
2.0434
1.9304
1.8184
1.7460
1.5794
1.5096
1.4541
1.4133
1.3576
1.2442
1.2333
1.2214
1.1915
0.7877
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.04
1.03
1.00
1.00
2.17
2.14
1.10
4.09
1.18
2.23
3.04
4.29


N
O
R*
R*
H
H
R*
S*
S*
O
H
Me

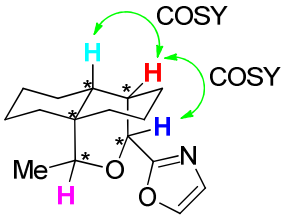
270

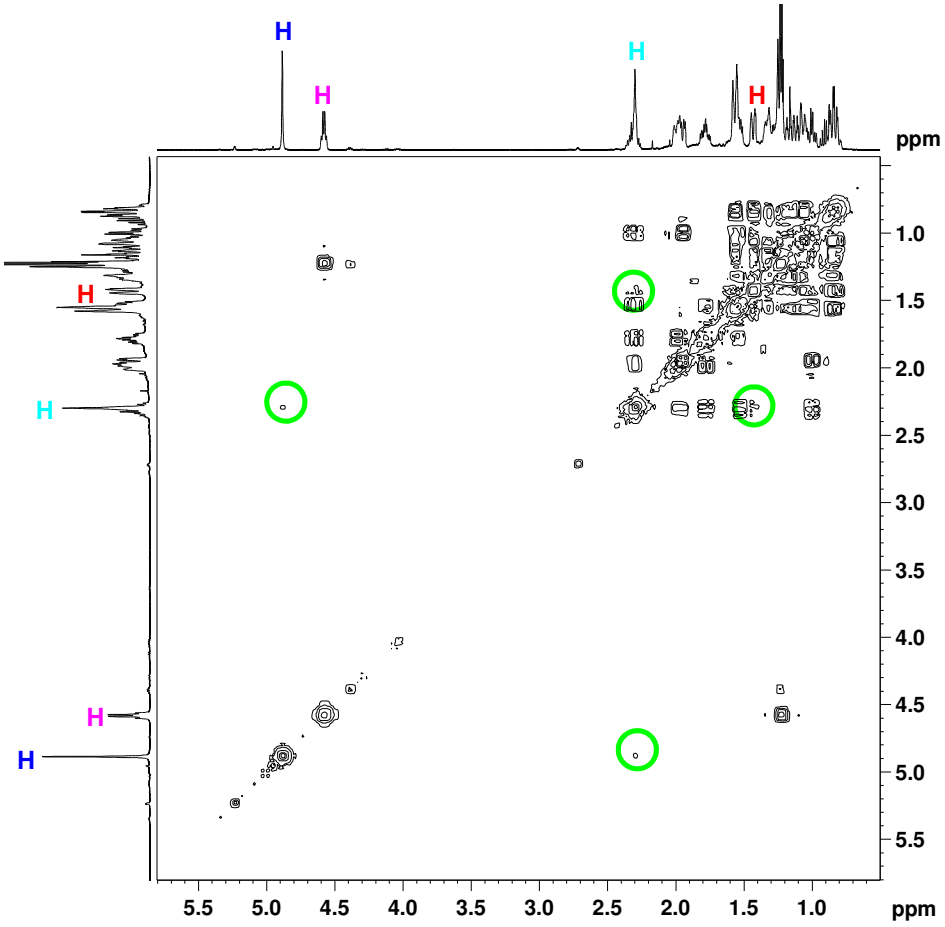

165.52
137.87
127.23
73.64
68.85
44.10
37.73
37.08
36.57
34.70
34.39
27.01
25.94
21.71
21.49
15.15
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

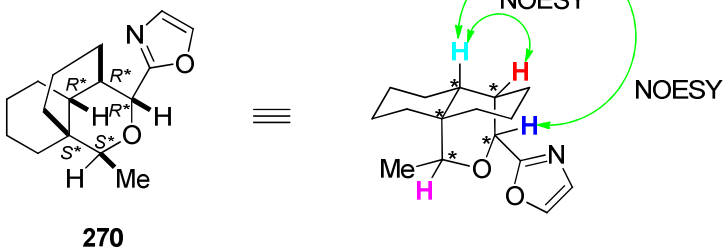

N
O
R*
R*
H
R*
H
S*
S*
O
H
Me

270

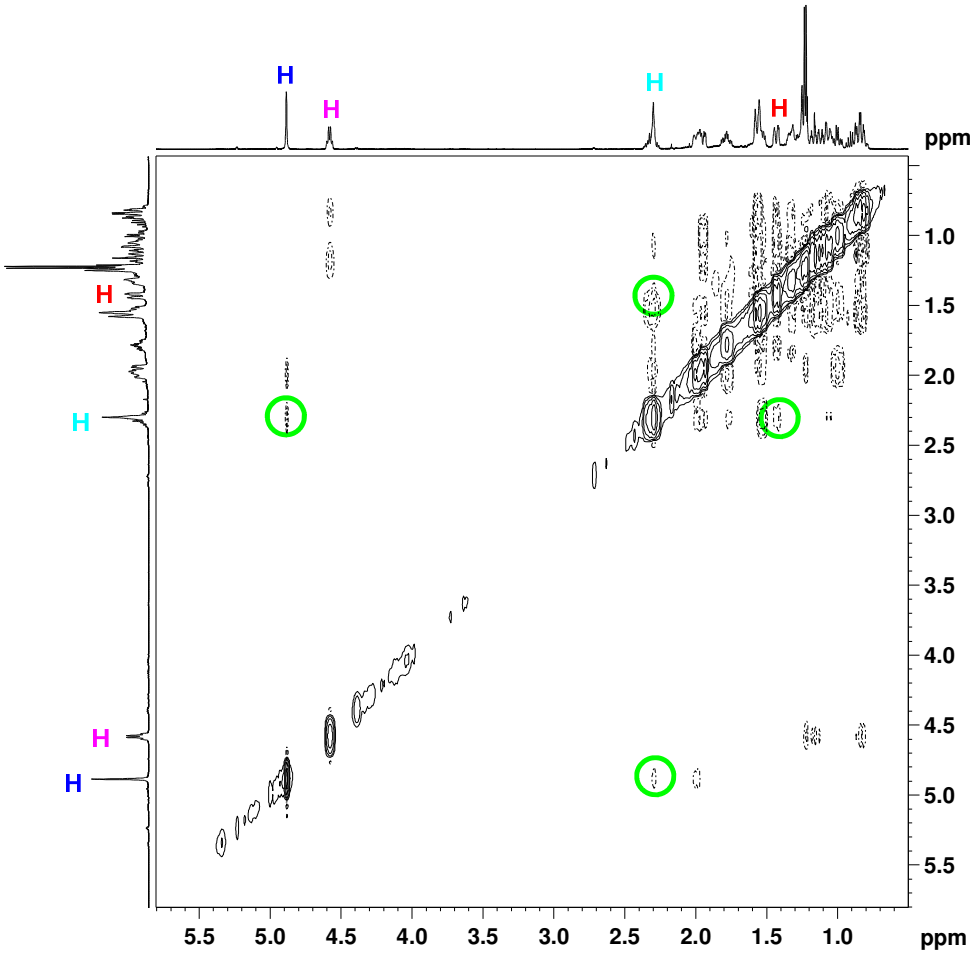
≡

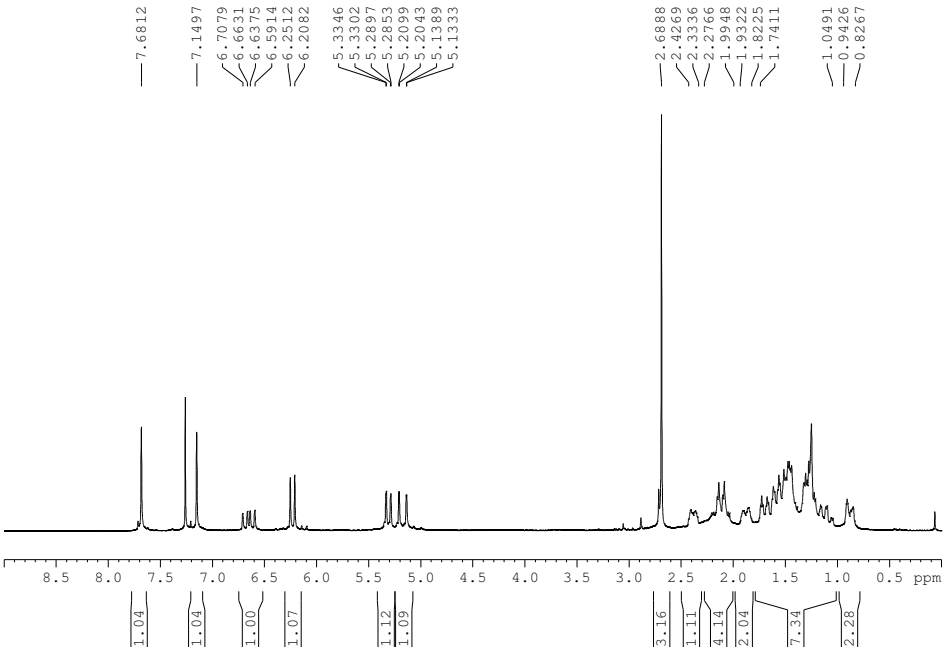

COSY
COSY
H
H
H
Me
H
O
N
O

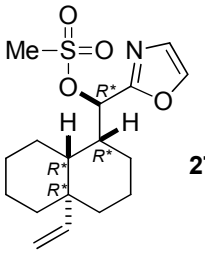

H
H
H
H
H
H
H
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


N
O
R*
R*
H
R*
H
S*
O
S*
H
Me
NOESY
H
H
H
Me
H
O
N
O
NOESY

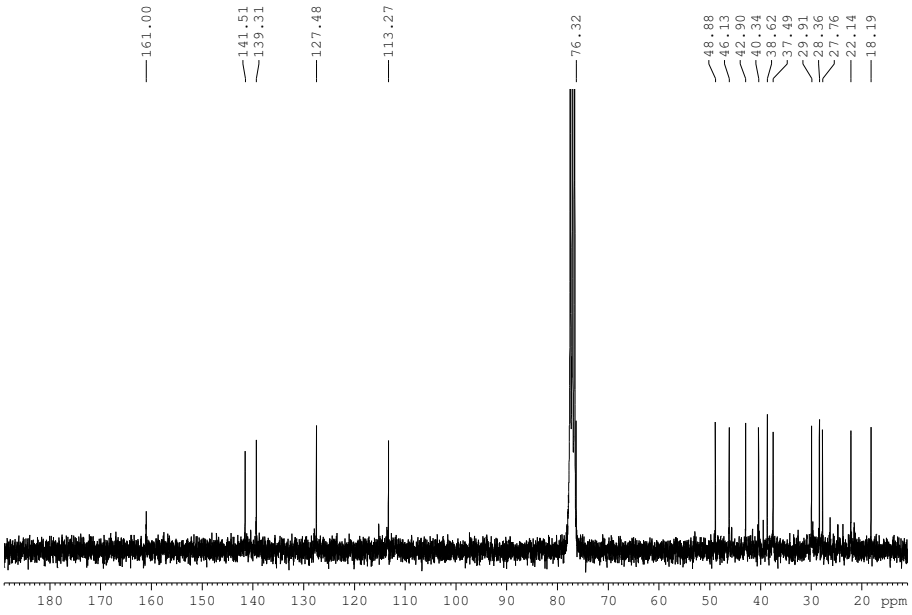
270

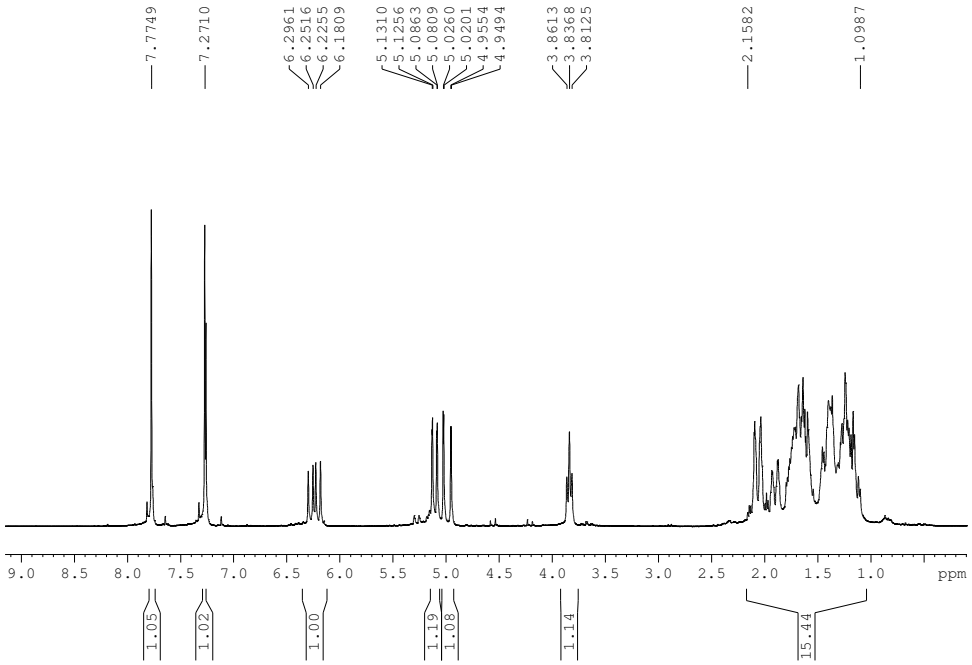

H
H
H
H
ppm
H
H
H
H
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

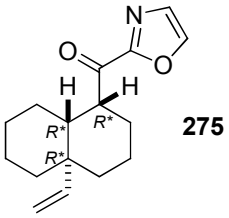

7.6812
7.1497
6.7079
6.6631
6.6375
6.5914
6.2512
6.2082
5.3346
5.3302
5.2897
5.2853
5.2099
5.2043
5.1389
5.1333
2.6888
2.4269
2.3336
2.2766
1.9948
1.9322
1.8225
1.7411
1.0491
0.9426
0.8267
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.04
1.04
1.00
1.07
1.12
1.09
3.16
1.11
4.14
2.04
7.34
2.28


O
Me−S=O
N
O
R*
O
H
H
R*
R*
R*

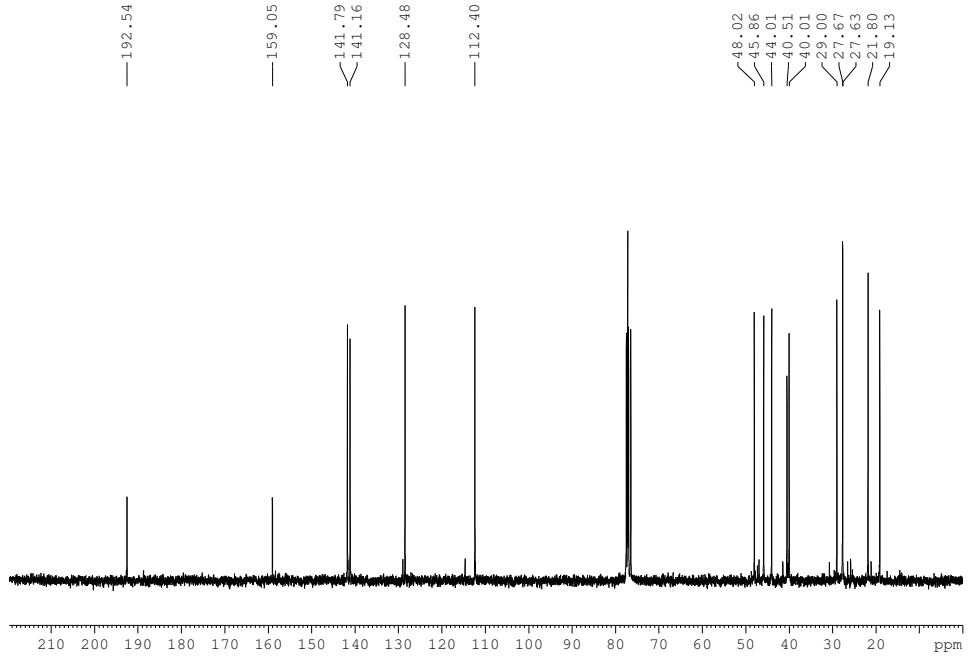
273

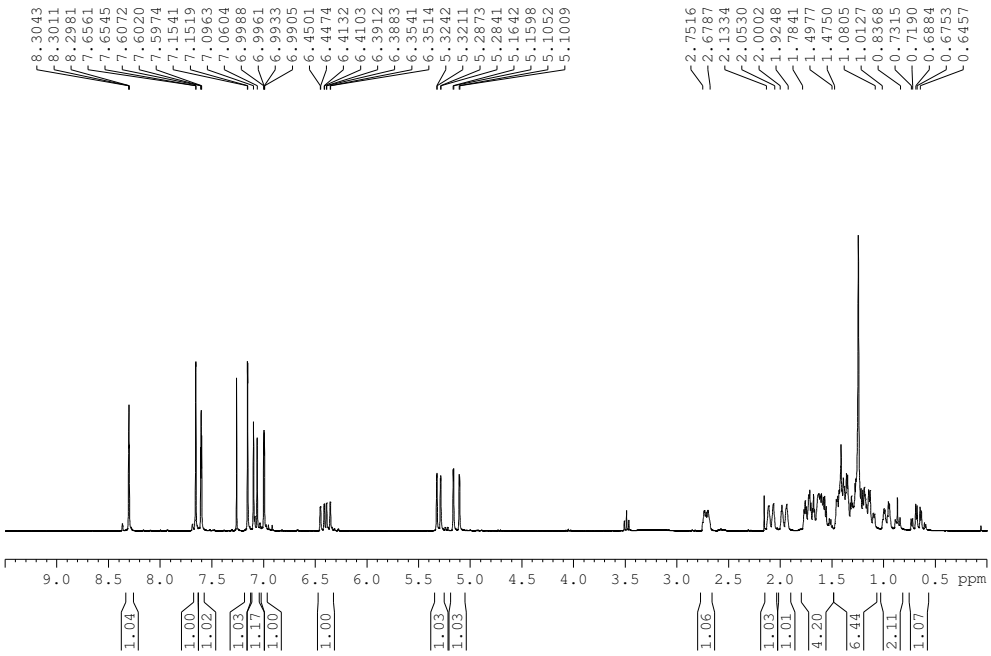

161.00
141.51
139.31
127.48
113.27
76.32
48.88
46.13
42.90
40.34
38.62
37.49
29.91
28.36
27.76
22.14
18.19
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

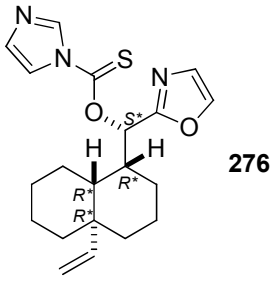

7.7749
7.2710
6.2961
6.2516
6.2255
6.1809
5.1310
5.1256
5.0863
5.0809
5.0260
5.0201
4.9554
4.9494
3.8613
3.8368
3.8125
2.1582
1.0987
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.05
1.02
1.00
1.19
1.08
1.14
15.44


N
O
O
H
H
R*
R*
R*

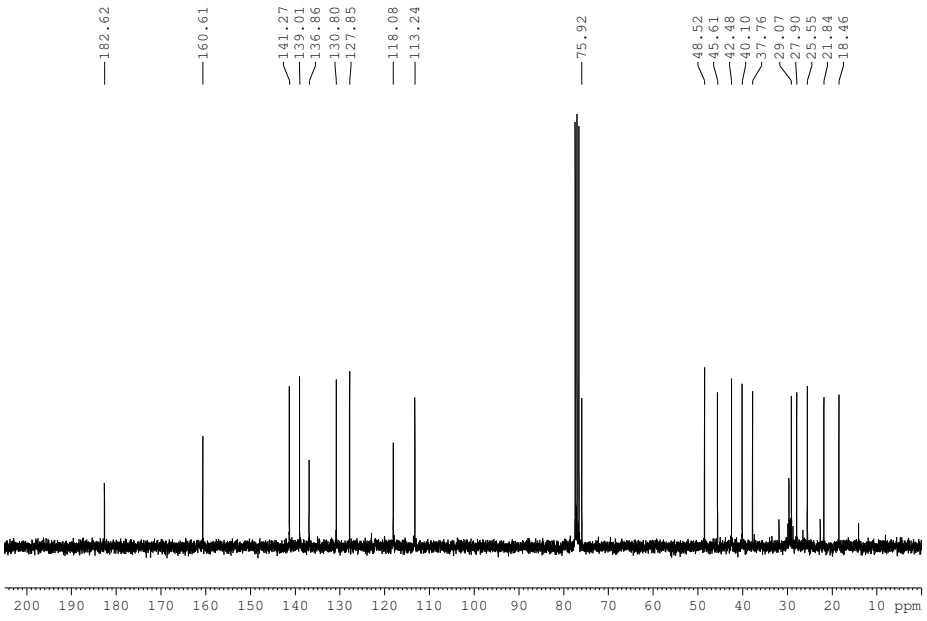
275

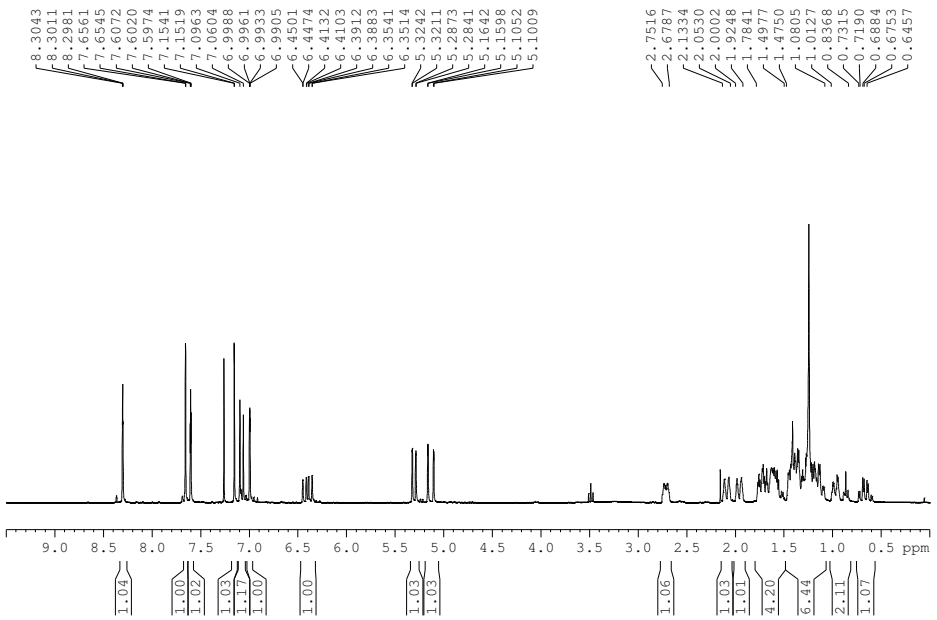

192.54
159.05
141.79
141.16
128.48
112.40
48.02
45.86
44.01
40.51
40.01
29.00
27.67
27.63
21.80
19.13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

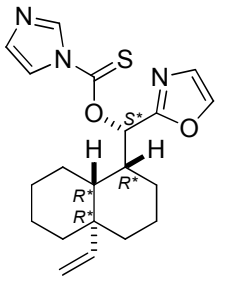

8.3043
8.3011
8.2981
7.6561
7.6545
7.6072
7.6020
7.5974
7.1541
7.1519
7.0963
7.0604
6.9988
6.9961
6.9933
6.9905
6.4501
6.4474
6.4132
6.4103
6.3912
6.3883
6.3541
6.3514
5.3242
5.3211
5.2873
5.2841
5.1642
5.1598
5.1052
5.1009
2.7516
2.6787
2.1334
2.0530
2.0002
1.9248
1.7841
1.4977
1.4750
1.0805
1.0127
0.8368
0.7315
0.7190
0.6884
0.6753
0.6457
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.04
1.00
1.02
1.03
1.17
1.00
1.00
1.03
1.03
1.06
1.03
1.01
4.20
6.44
2.11
1.07



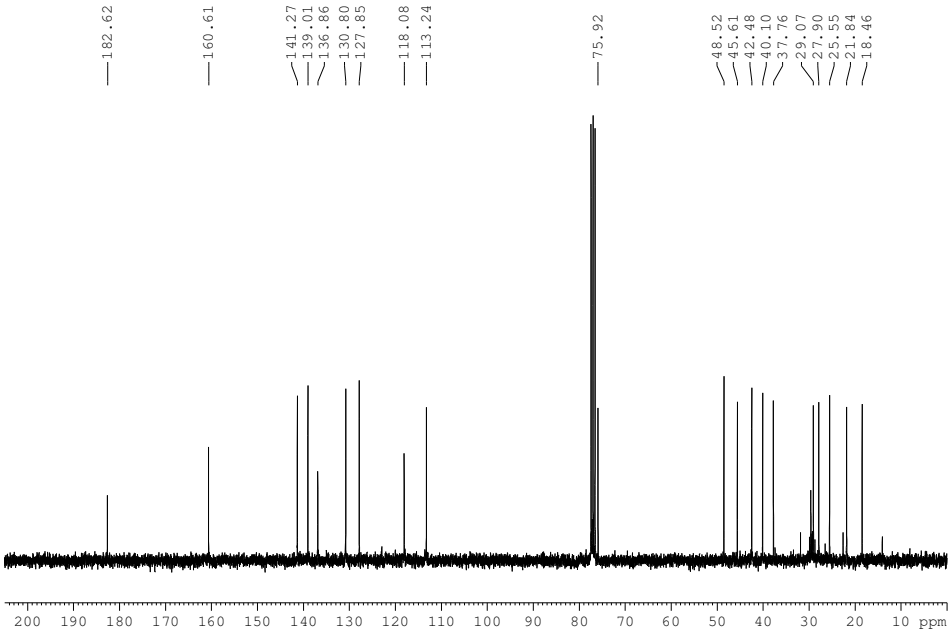
276

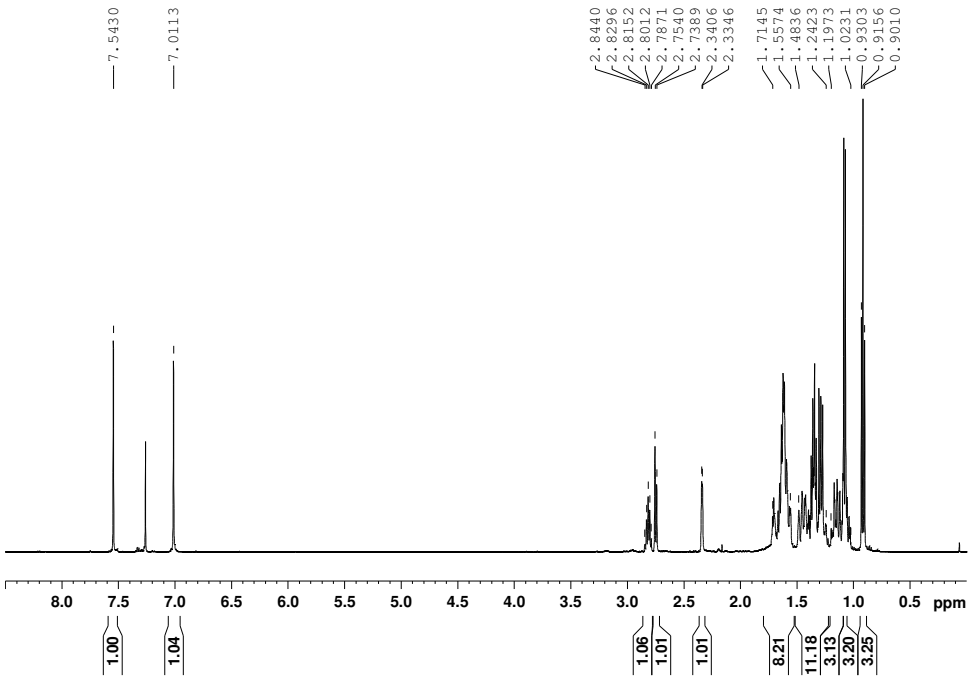

182.62
160.61
141.27
139.01
136.86
130.80
127.85
118.08
113.24
75.92
48.52
45.61
42.48
40.10
37.76
29.07
27.90
25.55
21.84
18.46
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

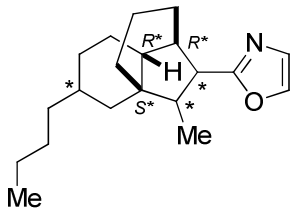

8.3043
8.3011
8.2981
7.6561
7.6545
7.6072
7.6020
7.5974
7.1541
7.1519
7.0963
7.0604
6.9988
6.9961
6.9933
6.9905
6.4501
6.4474
6.4132
6.4103
6.3912
6.3883
6.3541
6.3514
5.3242
5.3211
5.2873
5.2841
5.1642
5.1598
5.1052
5.1009
2.7516
2.6787
2.1334
2.0530
2.0002
1.9248
1.7841
1.4977
1.4750
1.0805
1.0127
0.8368
0.7315
0.7190
0.6884
0.6753
0.6457
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.04
1.00
1.02
1.03
1.17
1.00
1.00
1.03
1.03
1.06
1.03
1.01
4.20
6.44
2.11
1.07


N
N
S
O
S*
N
O
H
H
R*
R*
R*

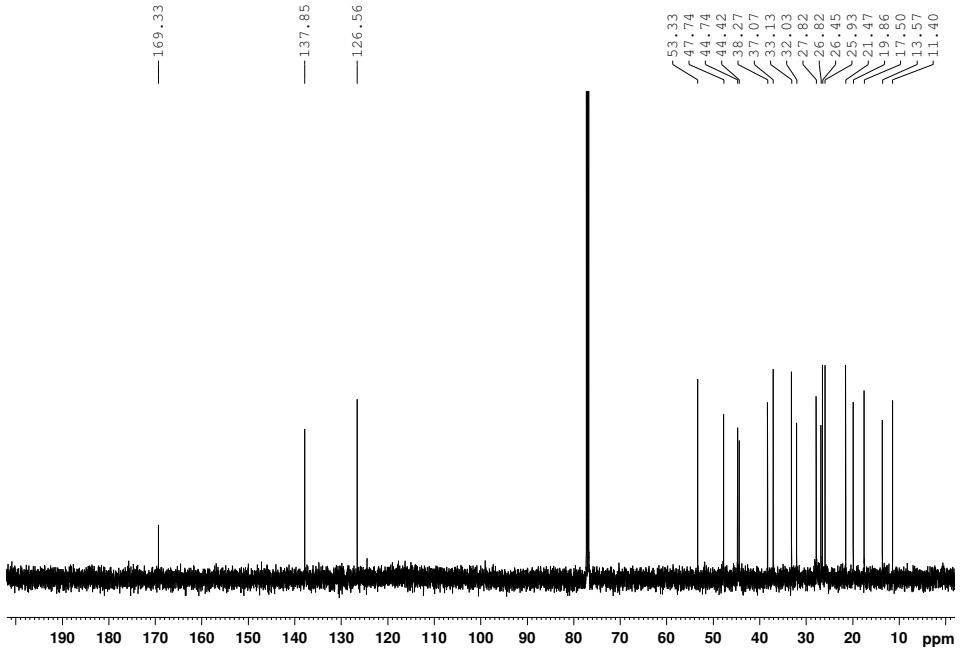
277

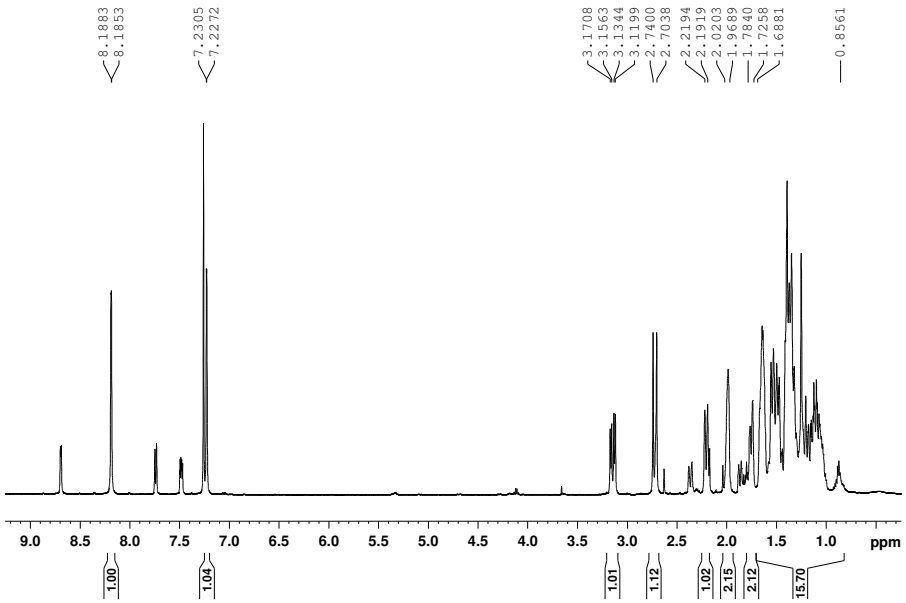

182.62
160.61
141.27
139.01
136.86
130.80
127.85
118.08
113.24
75.92
48.52
45.61
42.48
40.10
37.76
29.07
27.90
25.55
21.84
18.46
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

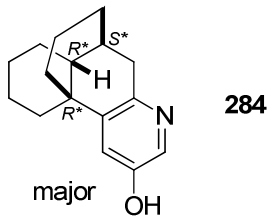

7.5430
7.0113
2.8440
2.8296
2.8152
2.8012
2.7871
2.7540
2.7389
2.3406
2.3346
1.7145
1.5574
1.4836
1.2423
1.1973
1.0231
0.9303
0.9156
0.9010
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.04
1.06
1.01
1.01
8.21
11.18
3.13
3.20
3.25


R*
R*
H
N
O
S*
Me
Me

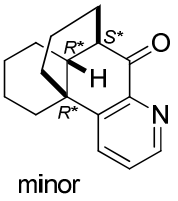
278


169.33
137.85
126.56
53.33
47.74
44.74
44.42
38.27
37.07
33.13
32.03
27.82
26.82
26.45
25.93
21.47
19.86
17.50
13.57
11.40
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

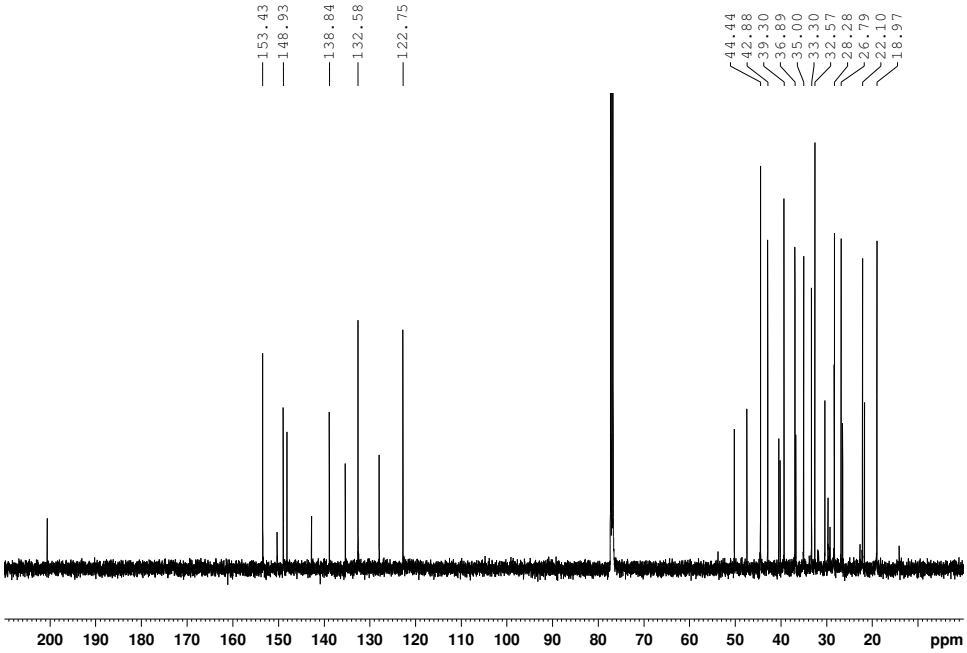

8.1883
8.1853
7.2305
7.2272
3.1708
3.1563
3.1344
3.1199
2.7400
2.7038
2.2194
2.1919
2.0203
1.9689
1.7840
1.7258
1.6881
0.8561
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.04
1.01
1.12
1.02
2.15
2.12
15.70

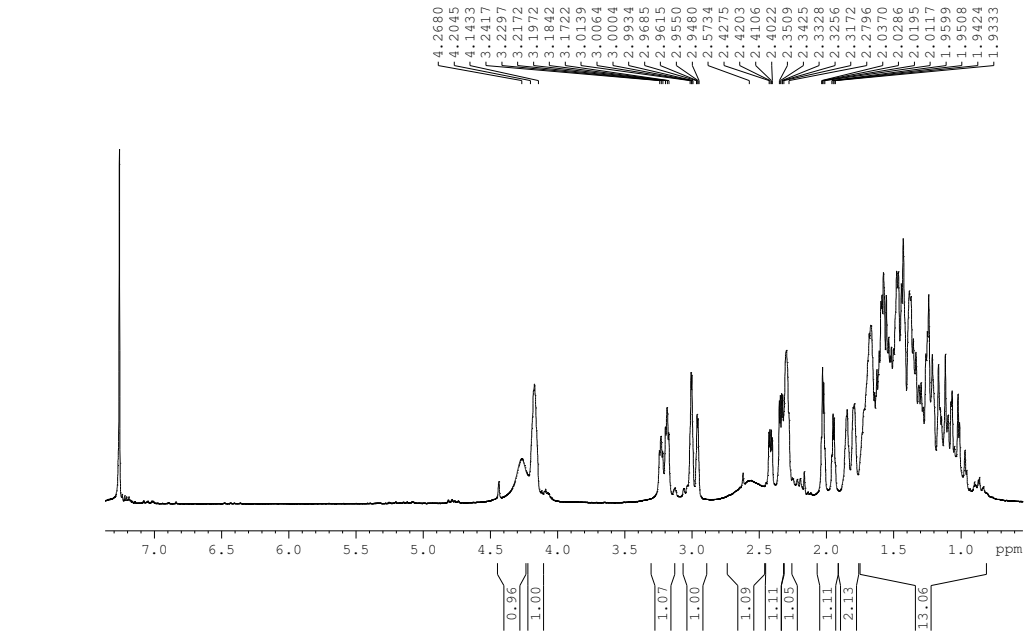

R*
S*
H
R*
N
major
OH

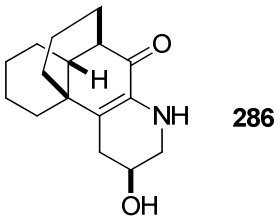
284


R*
S*
O
H
R*
N
minor

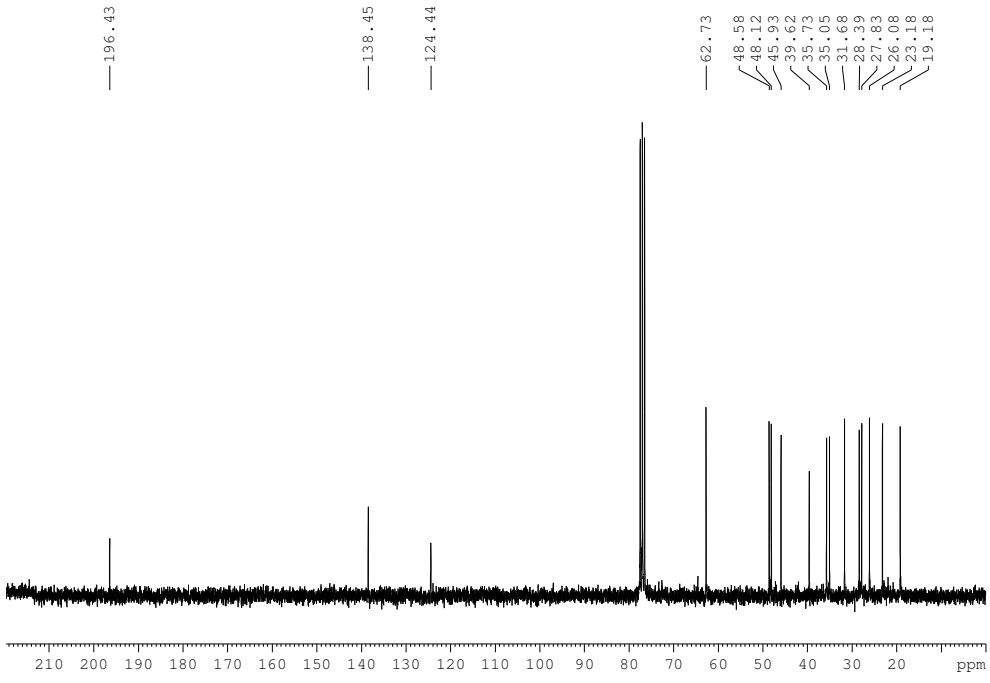
285

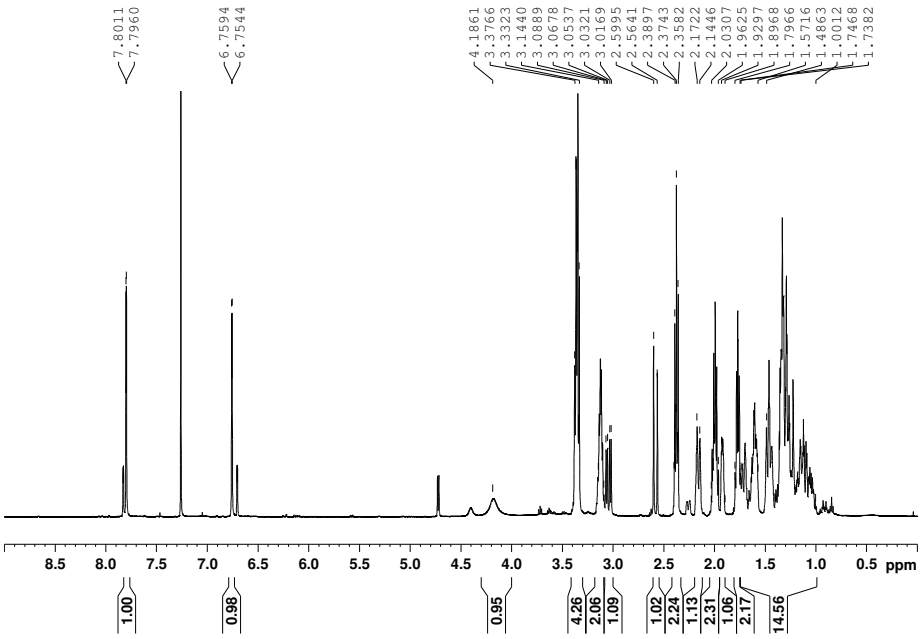

153.43
148.93
138.84
132.58
122.75
44.44
42.88
39.30
36.89
35.00
33.30
32.57
28.28
26.79
22.10
18.97
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

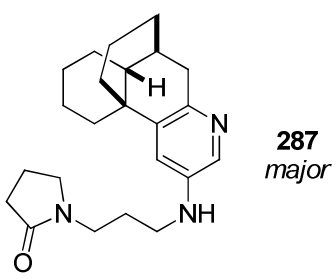

4.2680
4.2045
4.1433
3.2417
3.2297
3.2172
3.1972
3.1842
3.1722
3.0139
3.0064
3.0004
2.9934
2.9685
2.9615
2.9550
2.9480
2.5734
2.4275
2.4203
2.4106
2.4022
2.3509
2.3425
2.3328
2.3256
2.3172
2.2796
2.0370
2.0286
2.0195
2.0117
1.9599
1.9508
1.9424
1.9333
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.96
1.00
1.07
1.00
1.09
1.11
1.05
1.11
2.13
13.06


O
H
NH
OH

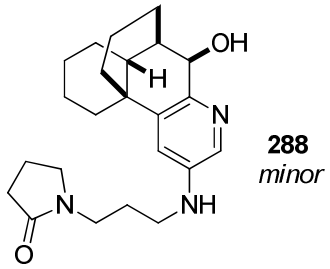
286


196.43
138.45
124.44
62.73
48.58
48.12
45.93
39.62
35.73
35.05
31.68
28.39
27.83
26.08
23.18
19.18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

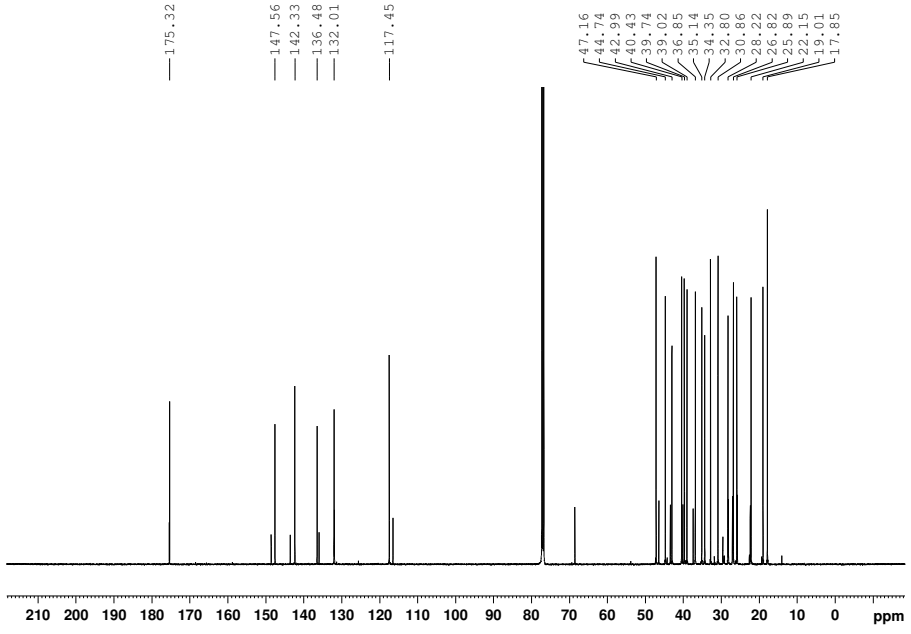


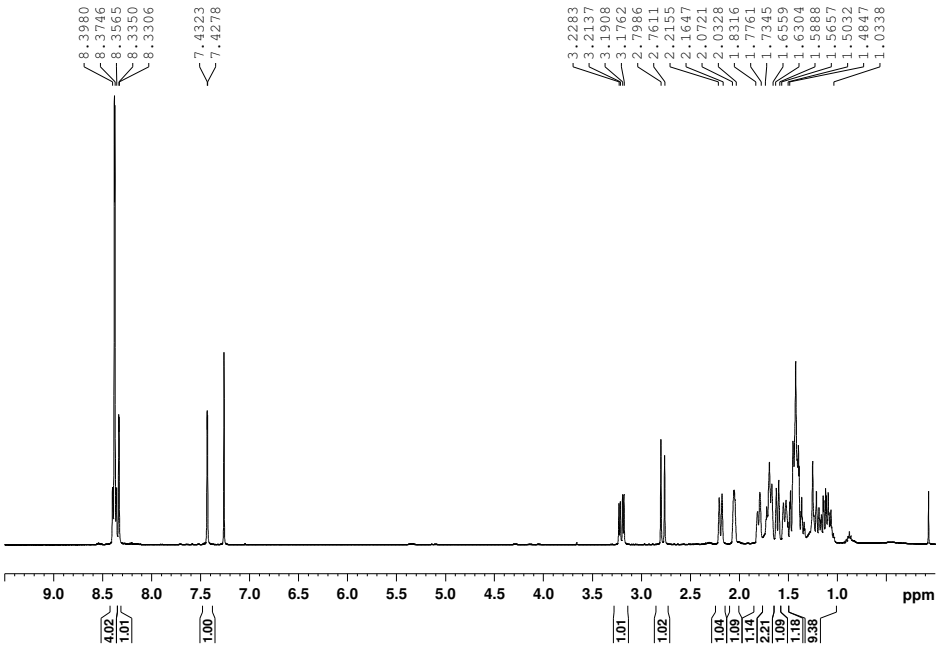


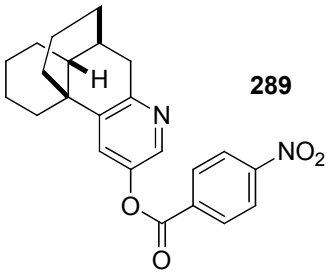
287
major



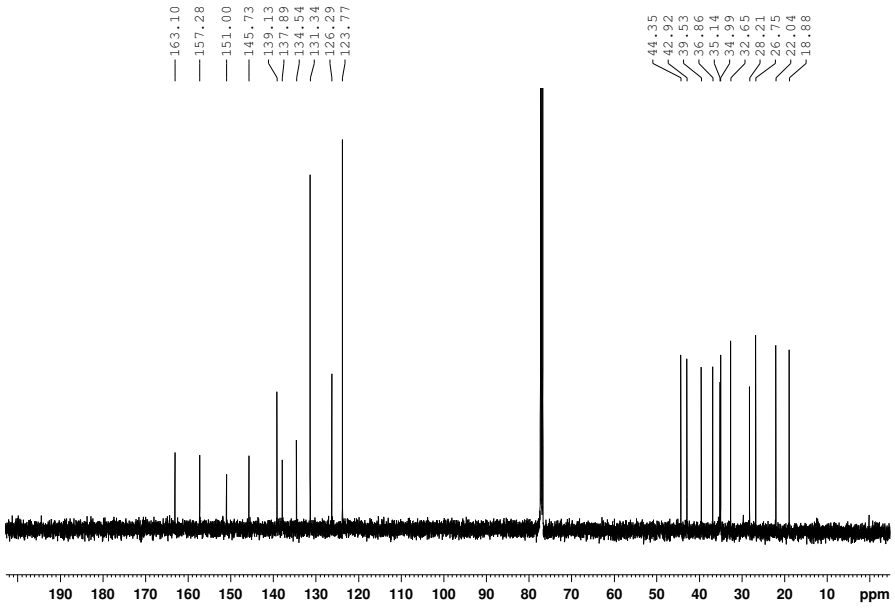
288
minor

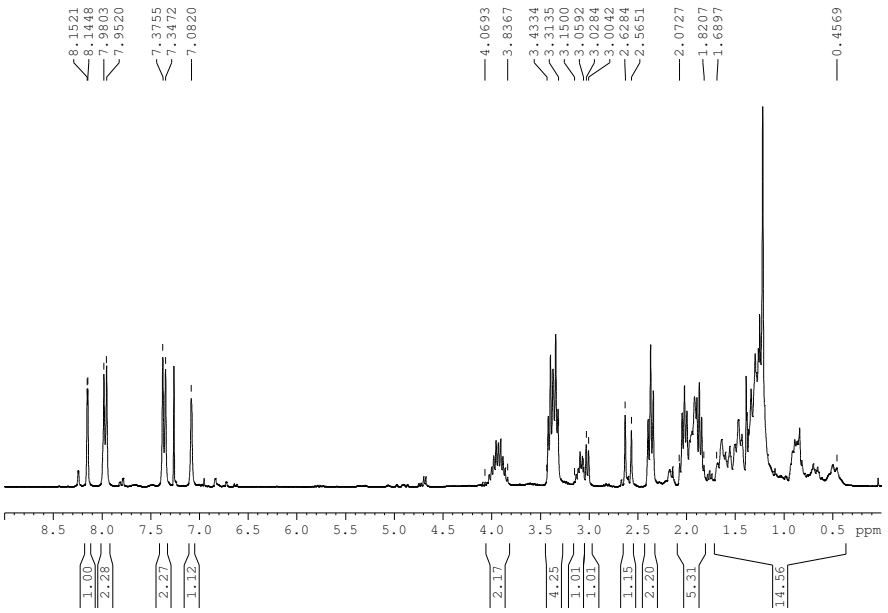


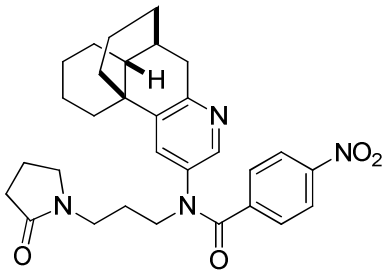

8.3980
8.3746
8.3565
8.3350
8.3306
7.4323
7.4278
3.2283
3.2137
3.1908
3.1762
2.7986
2.7611
2.2155
2.1647
2.0721
2.0328
1.8316
1.7761
1.7345
1.6559
1.6304
1.5888
1.5657
1.5032
1.4847
1.0338
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
4.02
1.01
1.00
1.01
1.02
1.04
1.09
1.14
2.21
1.09
1.18
9.38


H
N
O
O
NO2

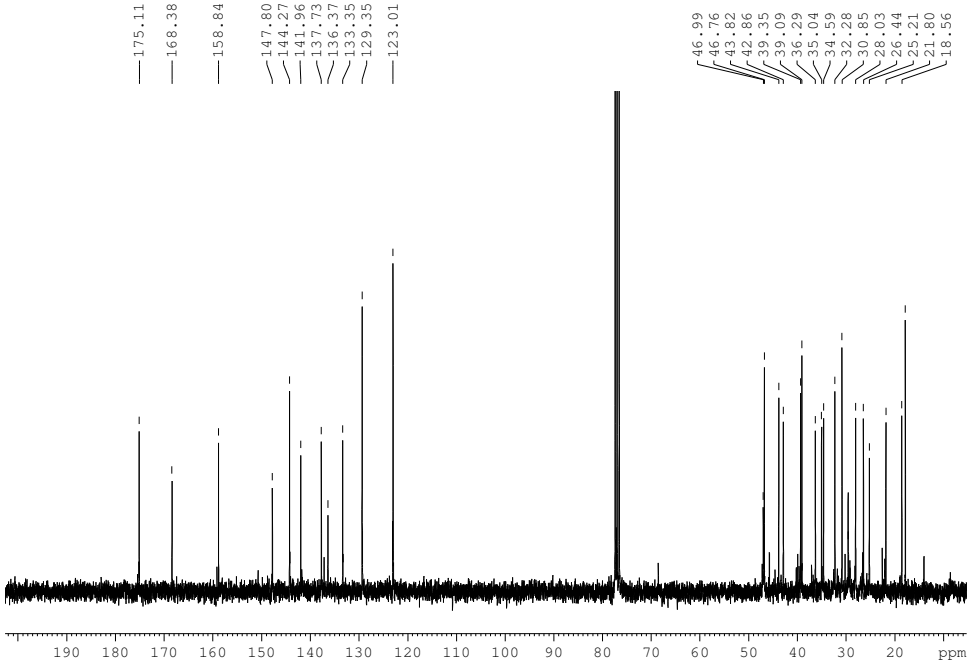
289

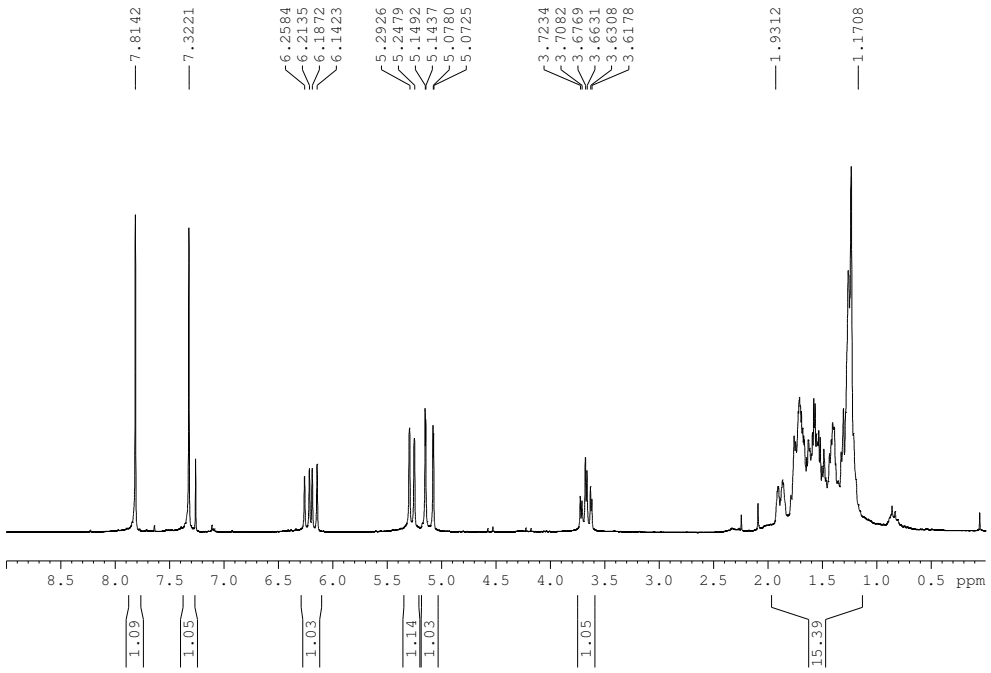

163.10
157.28
151.00
145.73
139.13
137.89
134.54
131.34
126.29
123.77
44.35
42.92
39.53
36.86
35.14
34.99
32.65
28.21
26.75
22.04
18.88
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

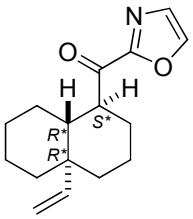

8.1521
8.1448
7.9803
7.9520
7.3755
7.3472
7.0820
4.0693
3.8367
3.4334
3.3135
3.1500
3.0592
3.0284
3.0042
2.6284
2.5651
2.0727
1.8207
1.6897
0.4569
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.28
2.27
1.12
2.17
4.25
1.01
1.01
1.15
2.20
5.31
14.56


H
N
NO2
N
N
O
O

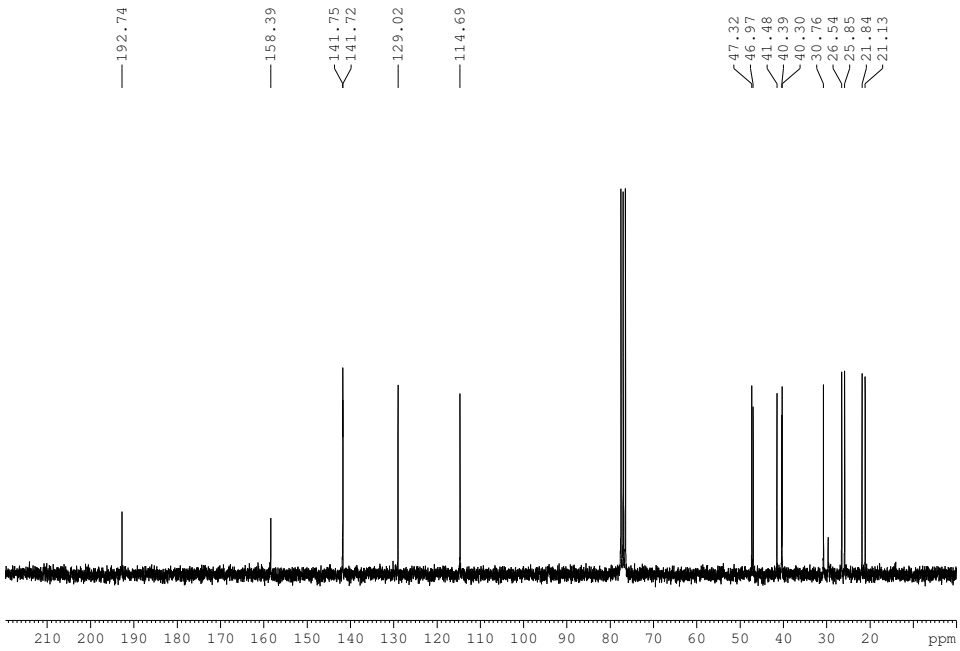
291

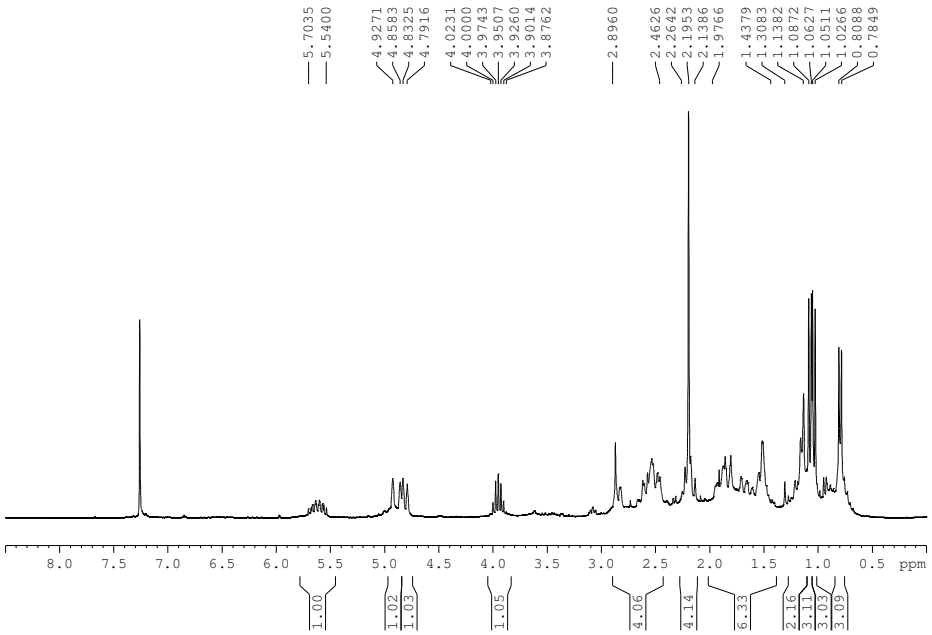

175.11
168.38
158.84
147.80
144.27
141.96
137.73
136.37
133.35
129.35
123.01
46.99
46.76
43.82
42.86
39.35
39.09
36.29
35.04
34.59
32.28
30.85
28.03
26.44
25.21
21.80
18.56
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

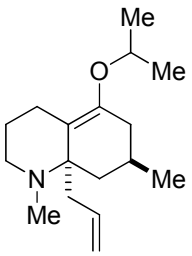

7.8142
7.3221
6.2584
6.2135
6.1872
6.1423
5.2926
5.2479
5.1492
5.1437
5.0780
5.0725
3.7234
3.7082
3.6769
3.6631
3.6308
3.6178
1.9312
1.1708
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.09
1.05
1.03
1.14
1.03
1.05
15.39


N
O
O
H
H
S*
R*
R*

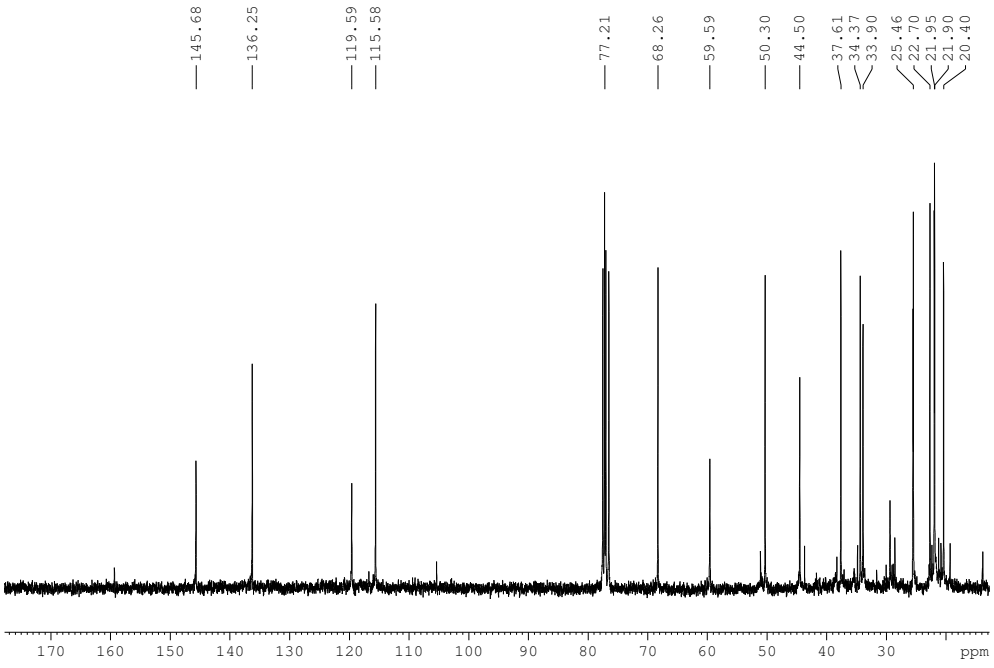
296

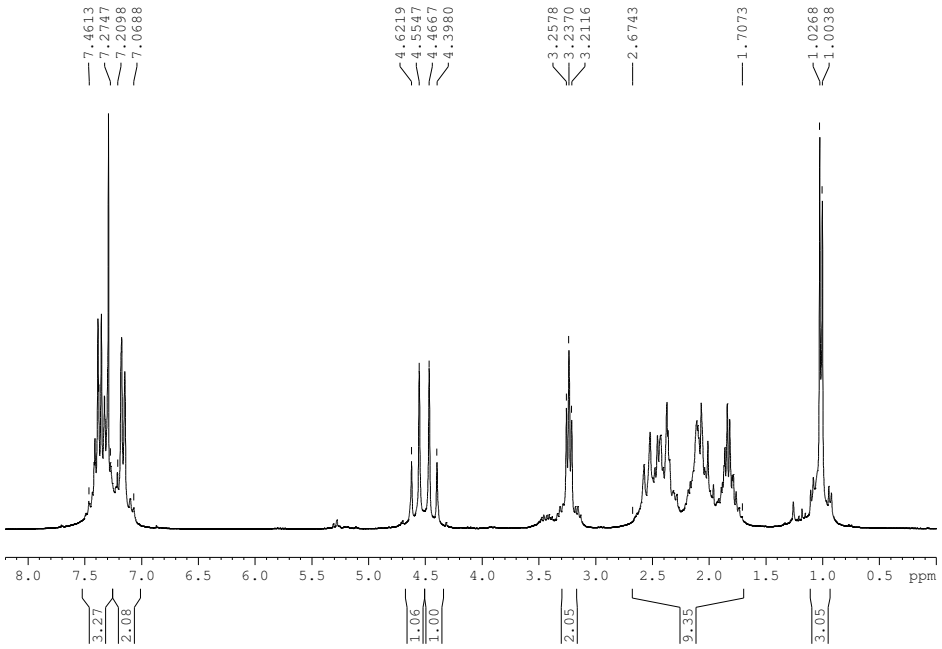

192.74
158.39
141.75
141.72
129.02
114.69
47.32
46.97
41.48
40.39
40.30
30.76
26.54
25.85
21.84
21.13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

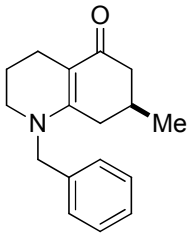

5.7035
5.5400
4.9271
4.8583
4.8325
4.7916
4.0231
4.0000
3.9743
3.9507
3.9260
3.9014
3.8762
2.8960
2.4626
2.2642
2.1953
2.1386
1.9766
1.4379
1.3083
1.1382
1.0872
1.0627
1.0511
1.0266
0.8088
0.7849
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.02
1.03
1.05
4.06
4.14
6.33
2.16
3.11
3.03
3.09


Me
O
Me
Me
N
Me

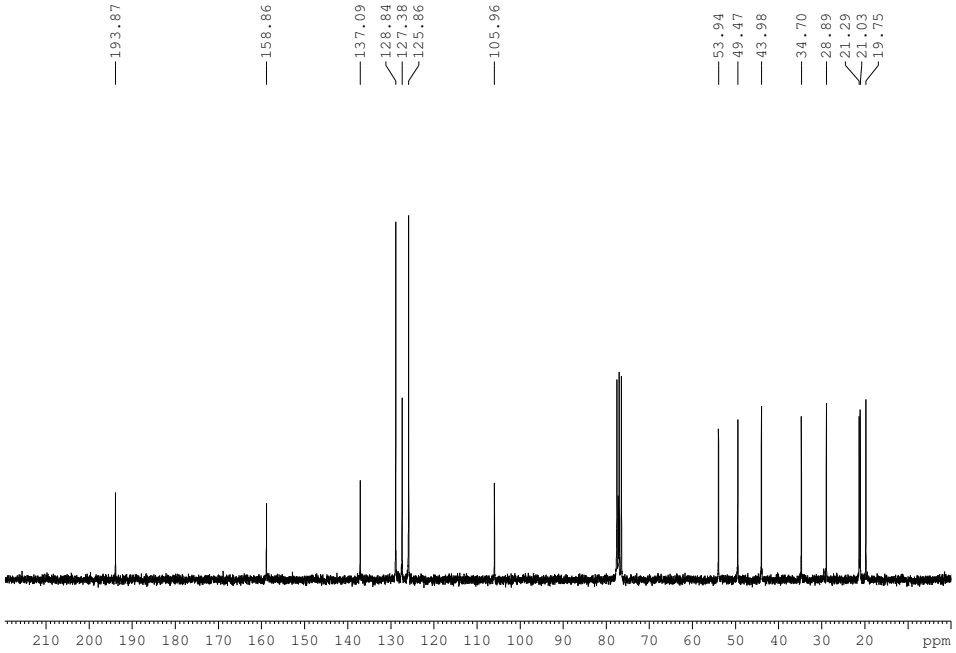
329

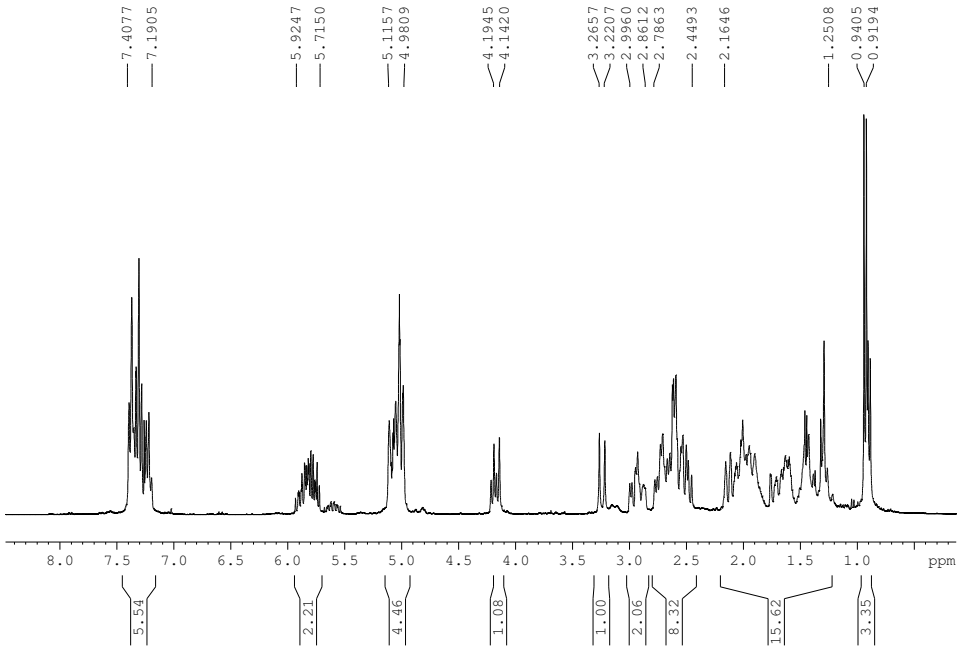

145.68
136.25
119.59
115.58
77.21
68.26
59.59
50.30
44.50
37.61
34.37
33.90
25.46
22.70
21.95
21.90
20.40
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

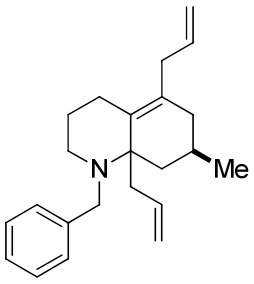

7.4613
7.2747
7.2098
7.0688
4.6219
4.5547
4.4667
4.3980
3.2578
3.2370
3.2116
2.6743
1.7073
1.0268
1.0038
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.27
2.08
1.06
1.00
2.05
9.35
3.05


O
N
Me

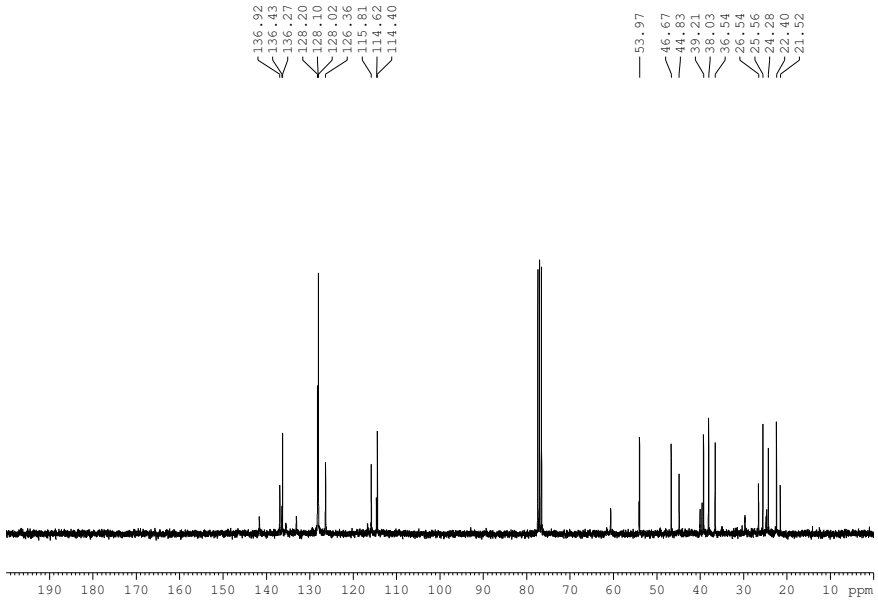
337

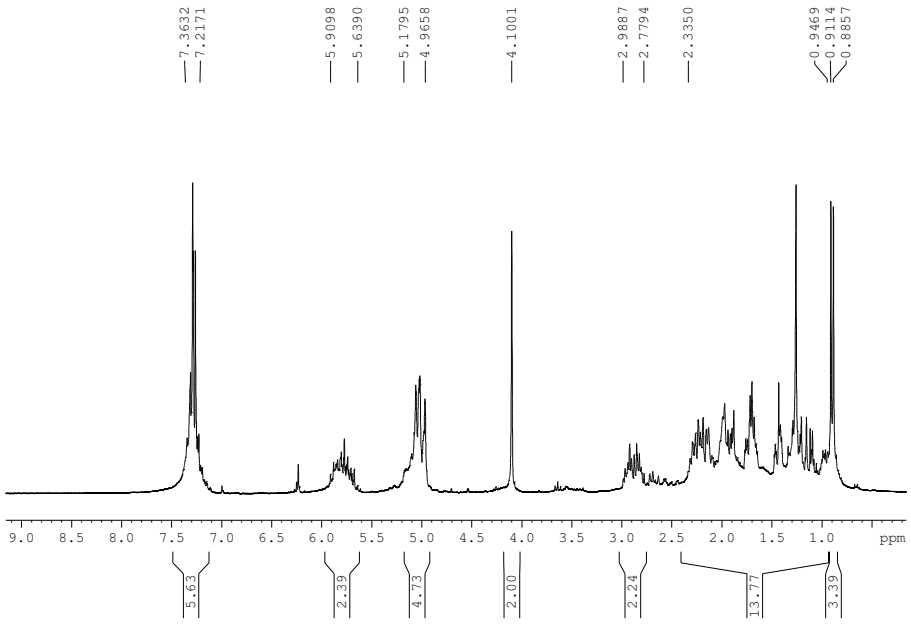

193.87
158.86
137.09
128.84
127.38
125.86
105.96
53.94
49.47
43.98
34.70
28.89
21.29
21.03
19.75
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

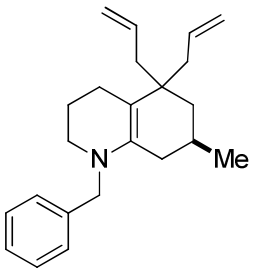

7.4077
7.1905
5.9247
5.7150
5.1157
4.9809
4.1945
4.1420
3.2657
3.2207
2.9960
2.8612
2.7863
2.4493
2.1646
1.2508
0.9405
0.9194
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
5.54
2.21
4.46
1.08
1.00
2.06
8.32
15.62
3.35


N
Me

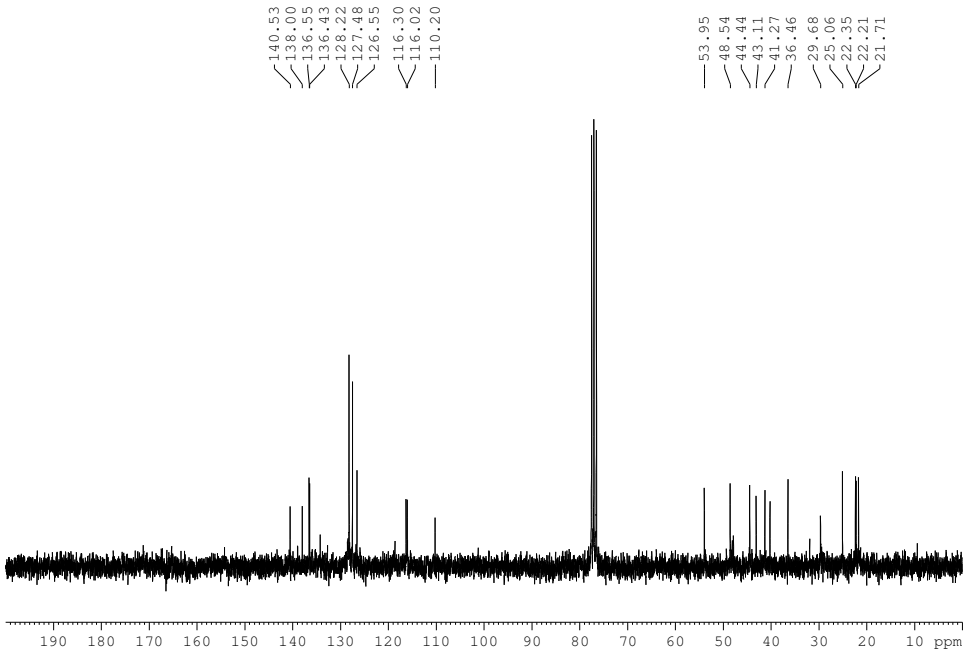
339

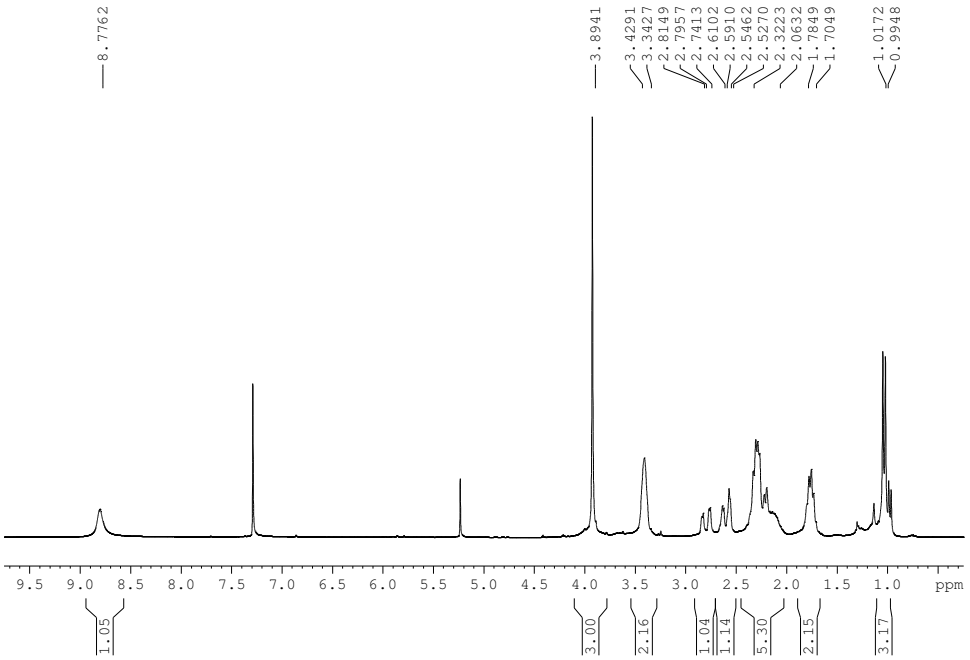

136.92
136.43
136.27
128.20
128.10
128.02
126.36
115.81
114.62
114.40
53.97
46.67
44.83
39.21
38.03
36.54
26.54
25.56
24.28
22.40
21.52
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

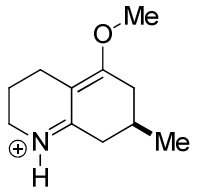

7.3632
7.2171
5.9098
5.6390
5.1795
4.9658
4.1001
2.9887
2.7794
2.3350
0.9469
0.9114
0.8857
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
5.63
2.39
4.73
2.00
2.24
13.77
3.39


N
Me

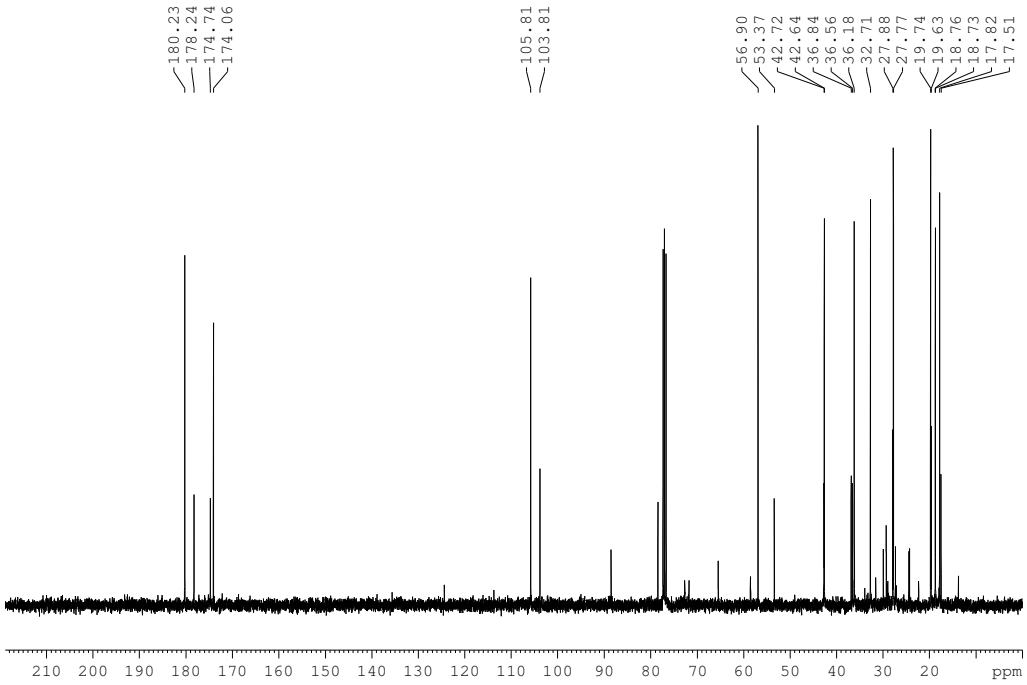
340

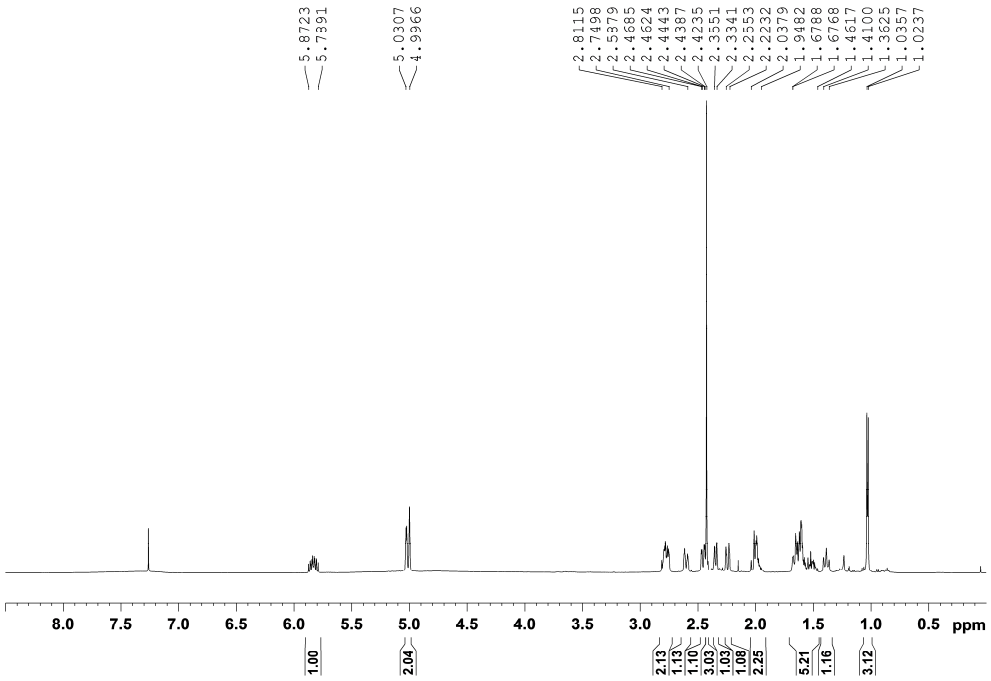

140.53
138.00
136.55
136.43
128.22
127.48
126.55
116.30
116.02
110.20
53.95
48.54
44.44
43.11
41.27
36.46
29.68
25.06
22.35
22.21
21.71
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.7762
3.8941
3.4291
3.3427
2.8149
2.7957
2.7413
2.6102
2.5910
2.5462
2.5270
2.3223
2.0632
1.7849
1.7049
1.0172
0.9948
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.05
3.00
2.16
1.04
1.14
5.30
2.15
3.17


Me
O
BF4
N
H
Me

341


180.23
178.24
174.74
174.06
105.81
103.81
56.90
53.37
42.72
42.64
36.84
36.56
36.18
32.71
27.88
27.77
19.74
19.63
18.76
18.73
17.82
17.51
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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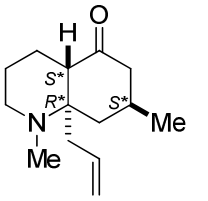
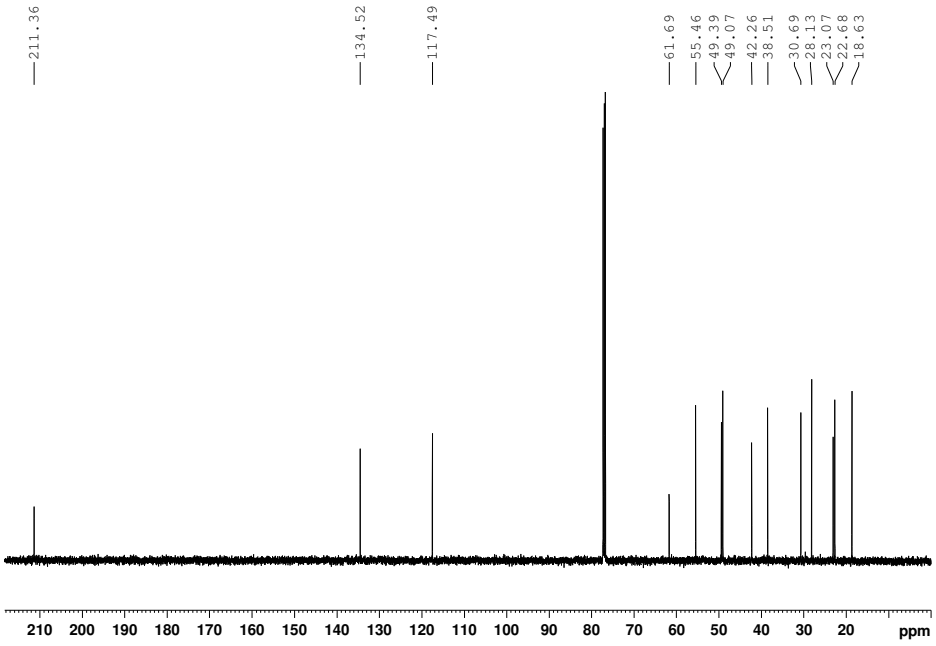
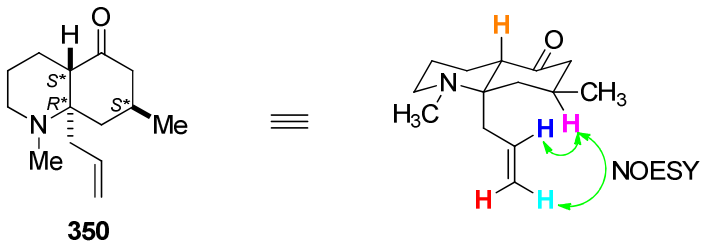
5.7391
5.0307
4.9966
2.8115
2.7498
2.5379
2.4685
2.4624
2.4443
2.4387
2.4235
2.3351
2.3341
2.2553
2.2232
2.0379
1.9482
1.6788
1.6768
1.4617
1.4100
1.3625
1.0357
1.0237
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.04
2.13
1.13
1.10
3.03
1.03
1.08
2.25
5.21
1.16
3.12

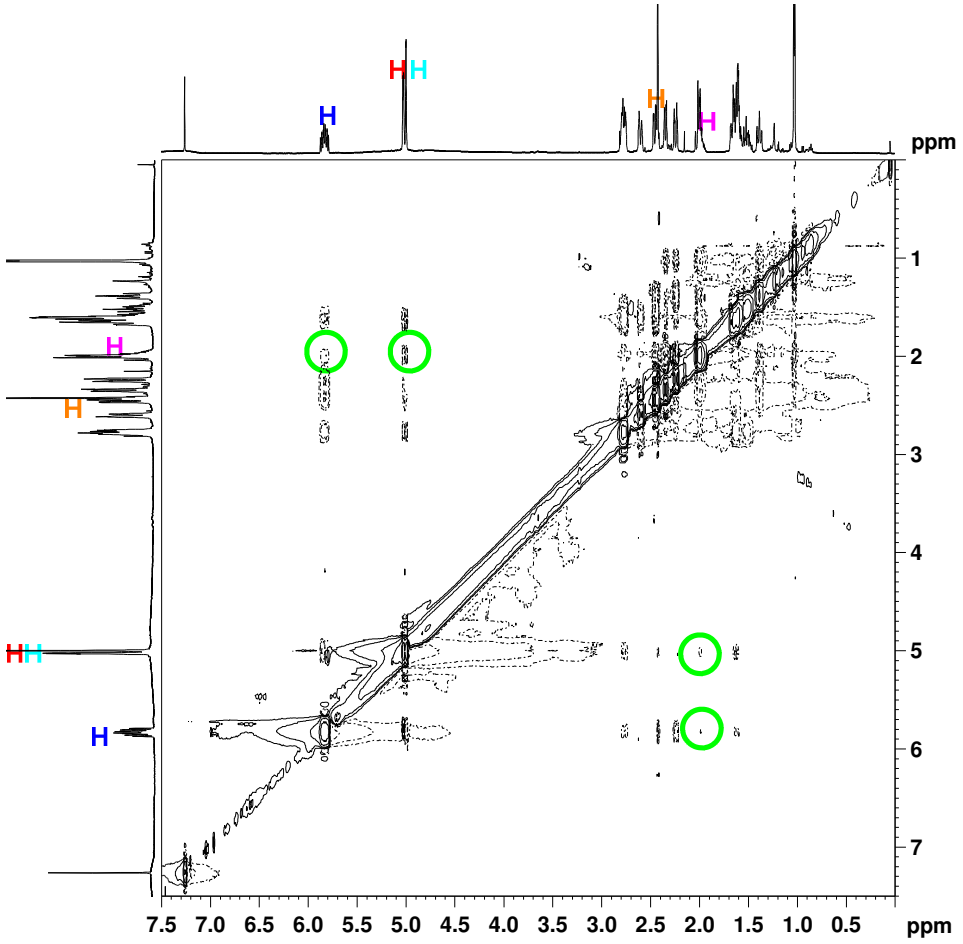

O
H
S*
R*
S*
Me
N
Me

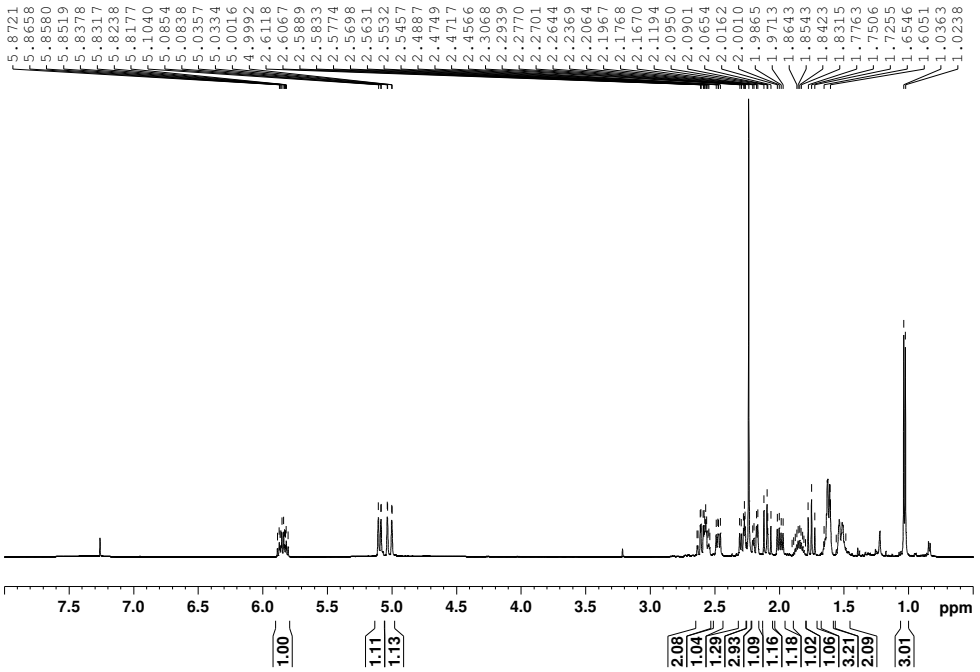
350


211.36
134.52
117.49
61.69
55.46
49.39
49.07
42.26
38.51
30.69
28.13
23.07
22.68
18.63
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


O
H
S*
R*
S*
N
Me
Me
H
O
N
CH3
H3C
H
H
NOESY
H
H

350


HH
H
H
H
H
HH
H
ppm
1
2
3
4
5
6
7
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm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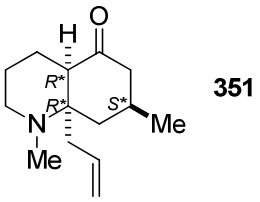
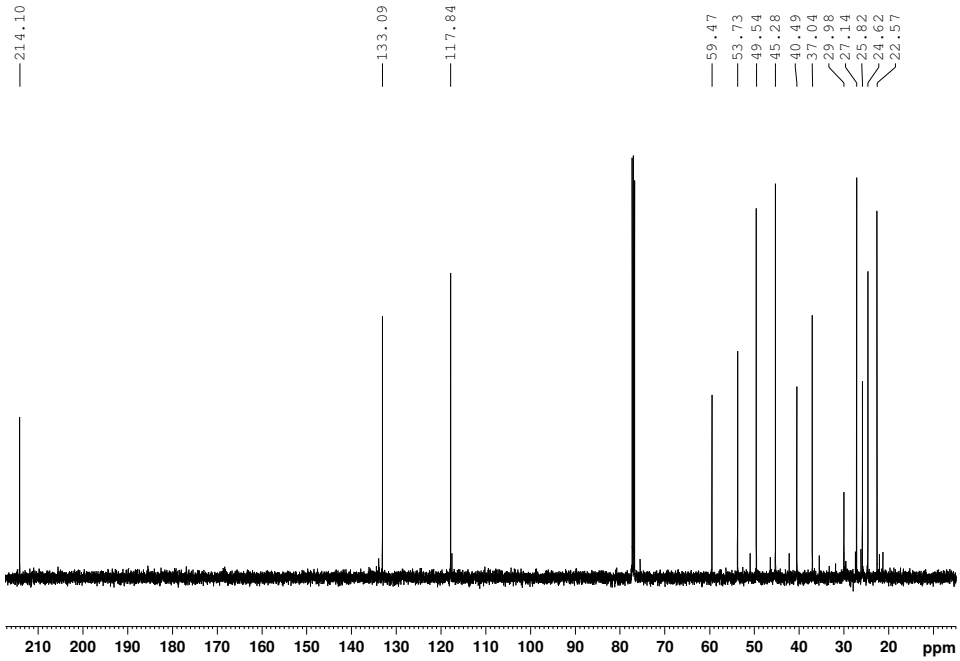
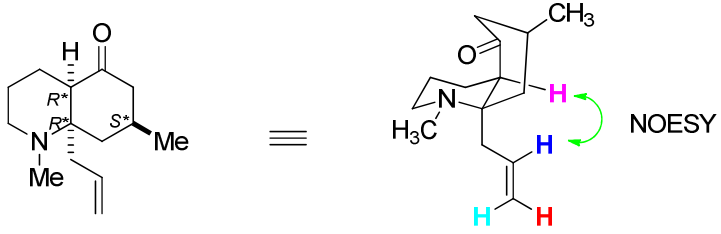
5.8580
5.8519
5.8378
5.8317
5.8238
5.8177
5.1040
5.0854
5.0838
5.0357
5.0334
5.0016
4.9992
2.6118
2.6067
2.5889
2.5833
2.5774
2.5698
2.5631
2.5532
2.5457
2.4887
2.4749
2.4717
2.4566
2.3068
2.2939
2.2770
2.2701
2.2644
2.2369
2.2064
2.1967
2.1768
2.1670
2.1194
2.0950
2.0901
2.0654
2.0162
2.0010
1.9865
1.9713
1.8643
1.8543
1.8423
1.8315
1.7763
1.7506
1.7255
1.6546
1.6051
1.0363
1.0238
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.11
1.13
2.08
1.04
1.29
2.93
1.09
1.16
1.18
1.02
1.06
3.21
2.09
3.01

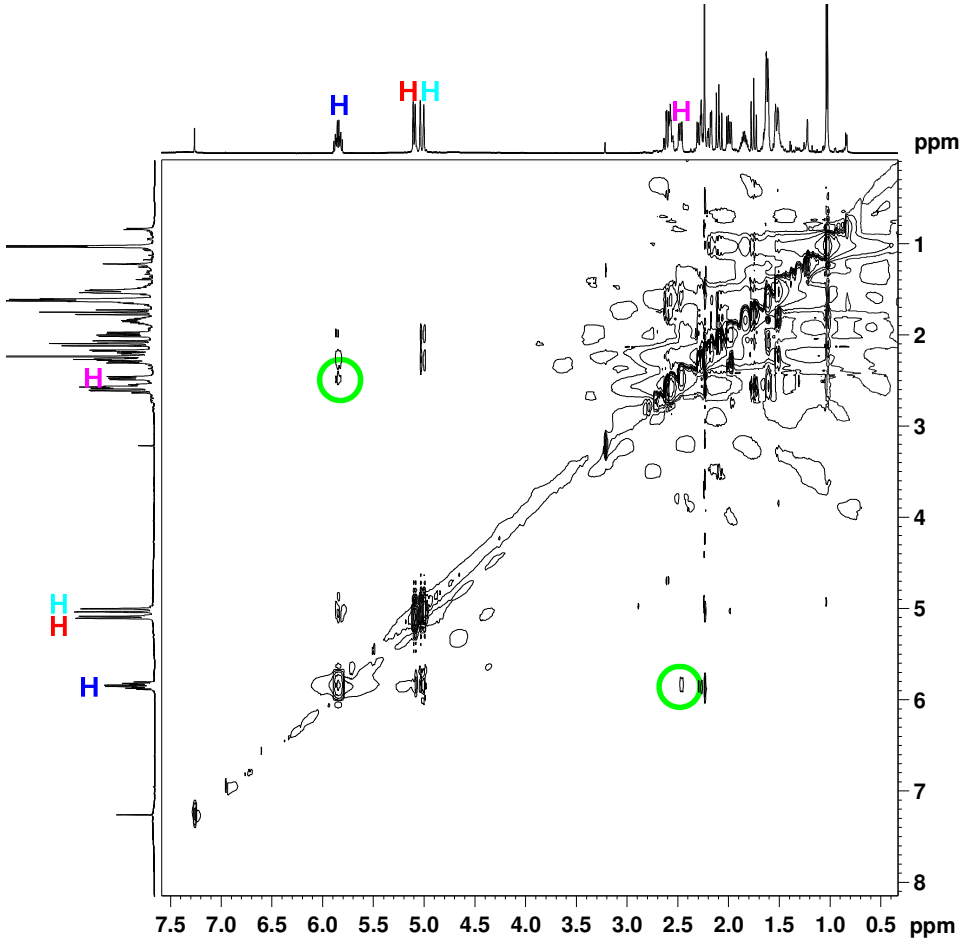

O
H
R*
R*
S*
Me
N
Me

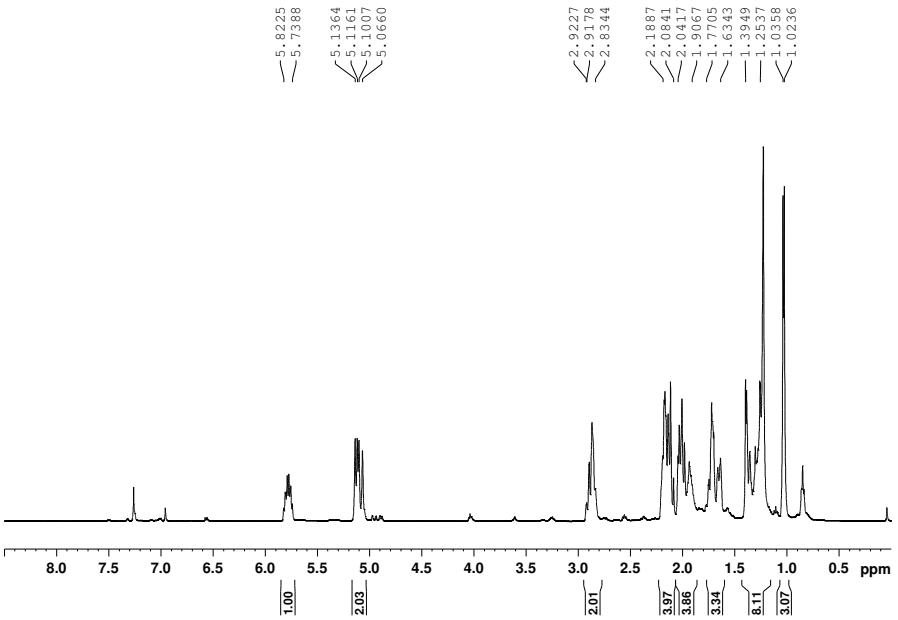
351


214.10
133.09
117.84
59.47
53.73
49.54
45.28
40.49
37.04
29.98
27.14
25.82
24.62
22.57
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


H
O
R*
R*
S*
N
Me
Me
CH3
O
N
H3C
H
H
H
H
NOESY

351


H
H
H
H
H
H
H
ppm
1
2
3
4
5
6
7
8
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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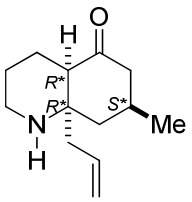
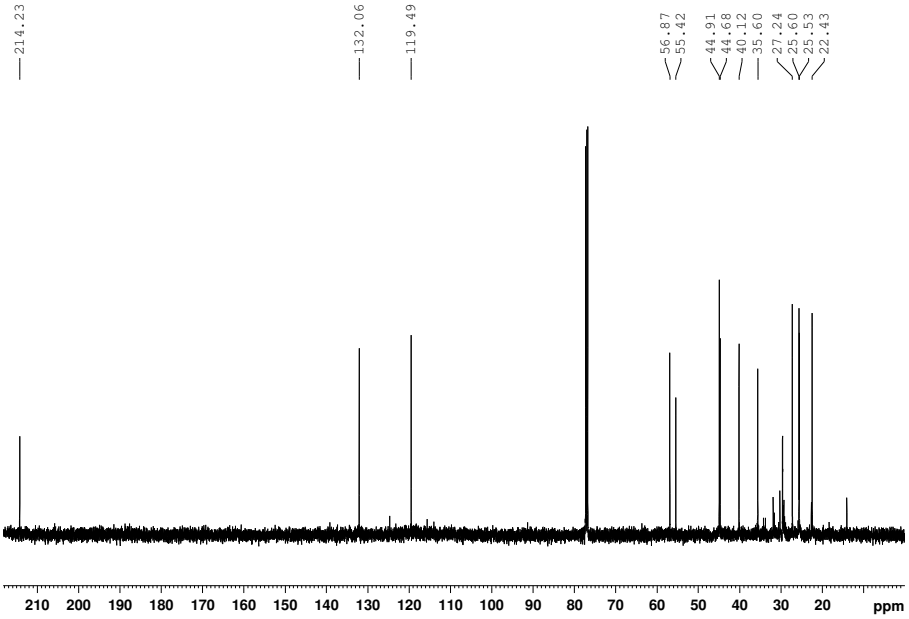
5.7388
5.1364
5.1161
5.1007
5.0660
2.9227
2.9178
2.8344
2.1887
2.0841
2.0417
1.9067
1.7705
1.6343
1.3949
1.2537
1.0358
1.0236
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.03
2.01
3.97
3.86
3.34
8.11
3.07


O
H
R*
R*
S*
Me
N
H

361


214.23
132.06
119.49
56.87
55.42
44.91
44.68
40.12
35.60
27.24
25.60
25.53
22.43
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

6.2 X-Ray Crystallography Data

Table 6.1 Crystal data and structure refinement for 177.

Identification code	h09sel3
Empirical formula	$C_{12}H_{20}O_2$
Formula weight	196.28
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 7.0510(2)Å α = 90°
	b = 13.9920(5)Å β = 91.091(2)°
	c = 11.0780(4)Å γ = 90°
Volume	1092.73(6) Å^3
Z	4
Density (calculated)	1.193 Mg/m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	432
Crystal size	0.35 x 0.35 x 0.30 mm
Theta range for data collection	3.68 to 27.50 °.
Index ranges	-9<=h<=9; -18<=k<=18; -14<=l<=14
Reflections collected	13960
Independent reflections	2477 [R(int) = 0.0469]
Reflections observed (>2σ)	2116
Data Completeness	0.987
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2477 / 0 / 130
Goodness-of-fit on F^2	1.073
Final R indices [I>2σ(I)]	R1 = 0.0569 wR2 = 0.1642
R indices (all data)	R1 = 0.0653 wR2 = 0.1732
Largest diff. peak and hole	0.783 and -0.258 eÅ^{-3}

Table 6.2 Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2 x 103) for 177. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	9912(2)	3715(1)	-485(1)	49(1)
O(2)	7036(2)	2691(1)	324(1)	48(1)
C(1)	8040(2)	2254(1)	1314(1)	36(1)
C(2)	8918(2)	1302(1)	946(2)	39(1)
C(3)	10719(2)	1432(1)	228(1)	34(1)
C(4)	12193(2)	2010(1)	941(1)	30(1)
C(5)	11442(2)	3014(1)	1281(1)	26(1)
C(6)	12817(2)	3498(1)	2183(1)	33(1)
C(7)	12094(2)	4467(1)	2605(2)	41(1)
C(8)	10146(2)	4388(1)	3167(2)	47(1)
C(9)	8744(2)	3881(1)	2313(2)	43(1)
C(10)	9520(2)	2904(1)	1929(1)	30(1)
C(11)	11358(2)	3586(1)	105(1)	31(1)
C(12)	13186(2)	3977(1)	-382(2)	46(1)

Table 6.3 Bond lengths [Å] and angles [o] for 177.

O(1)-C(11)	1.2139(18)	O(2)-C(1)	1.4312(19)
O(2)-H(2)	0.8400	C(1)-C(2)	1.528(2)
C(1)-C(10)	1.5333(19)	C(1)-H(1)	1.0000
C(2)-C(3)	1.522(2)	C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900	C(3)-C(4)	1.525(2)
C(3)-H(3A)	0.9900	C(3)-H(3B)	0.9900
C(4)-C(5)	1.5498(18)	C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900	C(5)-C(11)	1.5285(19)
C(5)-C(6)	1.5370(18)	C(5)-C(10)	1.5538(18)
C(6)-C(7)	1.525(2)	C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900	C(7)-C(8)	1.523(2)
C(7)-H(7A)	0.9900	C(7)-H(7B)	0.9900
C(8)-C(9)	1.530(2)	C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900	C(9)-C(10)	1.535(2)
C(9)-H(9A)	0.9900	C(9)-H(9B)	0.9900
C(10)-H(10)	1.0000	C(11)-C(12)	1.510(2)
C(12)-H(12A)	0.9800	C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800		
C(1)-O(2)-H(2)	109.5	O(2)-C(1)-C(2)	111.38(13)
O(2)-C(1)-C(10)	114.19(13)	C(2)-C(1)-C(10)	111.09(11)
O(2)-C(1)-H(1)	106.6	C(2)-C(1)-H(1)	106.6
C(10)-C(1)-H(1)	106.6	C(3)-C(2)-C(1)	112.41(12)
C(3)-C(2)-H(2A)	109.1	C(1)-C(2)-H(2A)	109.1
C(3)-C(2)-H(2B)	109.1	C(1)-C(2)-H(2B)	109.1
H(2A)-C(2)-H(2B)	107.9	C(2)-C(3)-C(4)	111.10(12)

C(2)-C(3)-H(3A)	109.4	C(4)-C(3)-H(3A)	109.4
C(2)-C(3)-H(3B)	109.4	C(4)-C(3)-H(3B)	109.4
H(3A)-C(3)-H(3B)	108.0	C(3)-C(4)-C(5)	111.92(11)
C(3)-C(4)-H(4A)	109.2	C(5)-C(4)-H(4A)	109.2
C(3)-C(4)-H(4B)	109.2	C(5)-C(4)-H(4B)	109.2
H(4A)-C(4)-H(4B)	107.9	C(11)-C(5)-C(6)	109.68(11)
C(11)-C(5)-C(4)	106.00(11)	C(6)-C(5)-C(4)	110.08(11)
C(11)-C(5)-C(10)	115.19(11)	C(6)-C(5)-C(10)	106.76(11)
C(4)-C(5)-C(10)	109.11(11)	C(7)-C(6)-C(5)	112.39(11)
C(7)-C(6)-H(6A)	109.1	C(5)-C(6)-H(6A)	109.1
C(7)-C(6)-H(6B)	109.1	C(5)-C(6)-H(6B)	109.1
H(6A)-C(6)-H(6B)	107.9	C(8)-C(7)-C(6)	111.69(13)
C(8)-C(7)-H(7A)	109.3	C(6)-C(7)-H(7A)	109.3
C(8)-C(7)-H(7B)	109.3	C(6)-C(7)-H(7B)	109.3
H(7A)-C(7)-H(7B)	107.9	C(7)-C(8)-C(9)	110.98(13)
C(7)-C(8)-H(8A)	109.4	C(9)-C(8)-H(8A)	109.4
C(7)-C(8)-H(8B)	109.4	C(9)-C(8)-H(8B)	109.4
H(8A)-C(8)-H(8B)	108.0	C(8)-C(9)-C(10)	110.79(13)
C(8)-C(9)-H(9A)	109.5	C(10)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5	C(10)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	108.1	C(1)-C(10)-C(9)	114.08(12)
C(1)-C(10)-C(5)	116.46(11)	C(9)-C(10)-C(5)	110.98(12)
C(1)-C(10)-H(10)	104.6	C(9)-C(10)-H(10)	104.6
C(5)-C(10)-H(10)	104.6	O(1)-C(11)-C(12)	117.85(14)
O(1)-C(11)-C(5)	123.75(13)	C(12)-C(11)-C(5)	118.34(12)
C(11)-C(12)-H(12A)	109.5	C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5	C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5	H(12B)-C(12)-H(12C)	109.5

Table 6.4 Anisotropic displacement parameters (Å2 x 103) for 177. The anisotropic displacement factor exponent takes the form: -2 gpi2 [h2 a*2 U11 + ... + 2 h k a* b* U].

Atom	U11	U22	U33	U23	U13	U12
O(1)	45(1)	55(1)	47(1)	19(1)	-13(1)	-1(1)
O(2)	29(1)	59(1)	56(1)	-2(1)	-9(1)	1(1)
C(1)	25(1)	41(1)	42(1)	-2(1)	1(1)	-4(1)
C(2)	35(1)	34(1)	47(1)	-3(1)	0(1)	-9(1)
C(3)	37(1)	29(1)	38(1)	-4(1)	0(1)	1(1)
C(4)	26(1)	27(1)	37(1)	1(1)	0(1)	4(1)
C(5)	22(1)	26(1)	30(1)	1(1)	-2(1)	2(1)
C(6)	27(1)	35(1)	37(1)	-2(1)	-6(1)	-2(1)
C(7)	43(1)	37(1)	43(1)	-9(1)	-5(1)	-5(1)
C(8)	47(1)	47(1)	47(1)	-18(1)	2(1)	3(1)
C(9)	33(1)	47(1)	49(1)	-13(1)	3(1)	7(1)
C(10)	25(1)	35(1)	31(1)	-3(1)	1(1)	0(1)
C(11)	34(1)	27(1)	33(1)	1(1)	0(1)	3(1)
C(12)	45(1)	44(1)	49(1)	11(1)	13(1)	1(1)

Table 6.5 Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2 x 103) for 177.

Atom	x	y	z	U(eq)
H(2)	7803	2991	-106	58
H(1)	7075	2104	1936	43
H(2A)	9216	923	1680	47
H(2B)	7982	937	453	47
H(3A)	10409	1765	-539	41
H(3B)	11252	798	30	41
H(4A)	13346	2081	453	36
H(4B)	12549	1659	1688	36
H(6A)	13007	3077	2893	39
H(6B)	14062	3585	1799	39
H(7A)	13003	4738	3205	50
H(7B)	12021	4910	1908	50
H(8A)	9666	5035	3352	57
H(8B)	10255	4027	3934	57
H(9A)	8513	4281	1588	52
H(9B)	7520	3792	2722	52
H(10)	9850	2573	2705	36
H(12A)	13032	4097	-1250	69
H(12B)	14206	3511	-245	69
H(12C)	13507	4576	32	69

Table 6.6 Dihedral angles [o] for 177.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
O(2) - C(1) - C(2) - C(3)	77.57(16)
C(10) - C(1) - C(2) - C(3)	-50.94(18)
C(1) - C(2) - C(3) - C(4)	57.60(17)
C(2) - C(3) - C(4) - C(5)	-59.08(16)
C(3) - C(4) - C(5) - C(11)	-71.58(14)
C(3) - C(4) - C(5) - C(6)	169.87(11)
C(3) - C(4) - C(5) - C(10)	53.02(15)
C(11) - C(5) - C(6) - C(7)	66.97(15)
C(4) - C(5) - C(6) - C(7)	-176.77(12)
C(10) - C(5) - C(6) - C(7)	-58.47(15)
C(5) - C(6) - C(7) - C(8)	56.85(17)
C(6) - C(7) - C(8) - C(9)	-53.31(19)
C(7) - C(8) - C(9) - C(10)	54.7(2)
O(2) - C(1) - C(10) - C(9)	52.36(17)
C(2) - C(1) - C(10) - C(9)	179.35(13)
O(2) - C(1) - C(10) - C(5)	-78.98(15)
C(2) - C(1) - C(10) - C(5)	48.01(17)
C(8) - C(9) - C(10) - C(1)	166.80(14)
C(8) - C(9) - C(10) - C(5)	-59.25(17)
C(11) - C(5) - C(10) - C(1)	70.32(16)
C(6) - C(5) - C(10) - C(1)	-167.65(12)
C(4) - C(5) - C(10) - C(1)	-48.72(15)
C(11) - C(5) - C(10) - C(9)	-62.44(15)
C(6) - C(5) - C(10) - C(9)	59.59(15)
C(4) - C(5) - C(10) - C(9)	178.52(11)
C(6) - C(5) - C(11) - O(1)	-141.19(15)
C(4) - C(5) - C(11) - O(1)	100.00(16)
C(10) - C(5) - C(11) - O(1)	-20.7(2)
C(6) - C(5) - C(11) - C(12)	41.60(17)
C(4) - C(5) - C(11) - C(12)	-77.21(15)
C(10) - C(5) - C(11) - C(12)	162.04(13)

Table 6.7 Crystal data and structure refinement for 193.

Identification code	k09sel2
Empirical formula	$C_{12}H_{22}O_2$
Formula weight	198.30
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 10.0480(2)Å α = 90°
	b = 8.1890(1)Å β = 105.657(1)°
	c = 14.2080(3)Å γ = 90°
Volume	1125.70(4) $Å^3$

Z	4
Density (calculated)	1.170 Mg/m^3
Absorption coefficient	0.077 mm^{-1}
F(000)	440
Crystal size	0.6 x 0.5 x 0.15 mm
Theta range for data collection	3.88 to 27.52°
Index ranges	-13<=h<=13; -10<=k<=10; -18<=l<=18
Reflections collected	20728
Independent reflections	2583 [R(int) = 0.0533]
Reflections observed (>2σ)	2255
Data Completeness	0.994
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.967 and 0.783
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2583 / 0 / 131
Goodness-of-fit on F^2	1.159
Final R indices [I>2σ(I)]	R1 = 0.0534 wR2 = 0.1344
R indices (all data)	R1 = 0.0601 wR2 = 0.1384
Largest diff. peak and hole	0.265 and -0.272 $eÅ^{-3}$

Table 6.8 Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2 x 103) for 193. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	934(1)	2472(2)	7174(1)	29(1)
O(2)	1023(1)	5149(1)	8191(1)	26(1)
C(1)	2319(2)	5874(2)	8163(1)	23(1)
C(2)	3484(2)	5026(2)	8912(1)	28(1)
C(3)	3692(2)	3270(2)	8619(1)	28(1)
C(4)	3934(2)	3199(2)	7598(1)	24(1)
C(5)	2835(2)	4067(2)	6780(1)	20(1)
C(6)	3454(2)	4383(2)	5908(1)	26(1)
C(7)	2511(2)	5402(2)	5088(1)	31(1)
C(8)	2112(2)	7023(2)	5473(1)	30(1)
C(9)	1554(2)	6806(2)	6371(1)	25(1)
C(10)	2575(2)	5800(2)	7151(1)	20(1)
C(11)	1498(2)	3021(2)	6403(1)	23(1)
C(12)	1682(2)	1492(2)	5846(1)	33(1)

Table 6.9 Bond lengths [Å] and angles [o] for 193.

O(1)-C(11)	1.435(2)	O(1)-H(1)	0.8400
O(2)-C(1)	1.4417(19)	O(2)-H(2)	0.8400
C(1)-C(2)	1.520(2)	C(1)-C(10)	1.529(2)
C(1)-H(1A)	1.0000	C(2)-C(3)	1.527(3)
C(2)-H(2A)	0.9900	C(2)-H(2B)	0.9900
C(3)-C(4)	1.536(2)	C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900	C(4)-C(5)	1.544(2)
C(4)-H(4A)	0.9900	C(4)-H(4B)	0.9900
C(5)-C(6)	1.551(2)	C(5)-C(10)	1.560(2)
C(5)-C(11)	1.561(2)	C(6)-C(7)	1.534(2)
C(6)-H(6A)	0.9900	C(6)-H(6B)	0.9900
C(7)-C(8)	1.530(3)	C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900	C(8)-C(9)	1.537(2)
C(8)-H(8A)	0.9900	C(8)-H(8B)	0.9900
C(9)-C(10)	1.531(2)	C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900	C(10)-H(10)	1.0000
C(11)-C(12)	1.519(2)	C(11)-H(11)	1.0000
C(12)-H(12A)	0.9800	C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800		
C(11)-O(1)-H(1)	109.5	C(1)-O(2)-H(2)	109.5
O(2)-C(1)-C(2)	108.84(14)	O(2)-C(1)-C(10)	113.09(13)
C(2)-C(1)-C(10)	110.31(13)	O(2)-C(1)-H(1A)	108.2
C(2)-C(1)-H(1A)	108.2	C(10)-C(1)-H(1A)	108.2
C(1)-C(2)-C(3)	112.04(14)	C(1)-C(2)-H(2A)	109.2
C(3)-C(2)-H(2A)	109.2	C(1)-C(2)-H(2B)	109.2
C(3)-C(2)-H(2B)	109.2	H(2A)-C(2)-H(2B)	107.9
C(2)-C(3)-C(4)	111.22(14)	C(2)-C(3)-H(3A)	109.4
C(4)-C(3)-H(3A)	109.4	C(2)-C(3)-H(3B)	109.4
C(4)-C(3)-H(3B)	109.4	H(3A)-C(3)-H(3B)	108.0
C(3)-C(4)-C(5)	115.46(13)	C(3)-C(4)-H(4A)	108.4
C(5)-C(4)-H(4A)	108.4	C(3)-C(4)-H(4B)	108.4
C(5)-C(4)-H(4B)	108.4	H(4A)-C(4)-H(4B)	107.5
C(4)-C(5)-C(6)	108.58(12)	C(4)-C(5)-C(10)	108.40(13)
C(6)-C(5)-C(10)	104.97(13)	C(4)-C(5)-C(11)	112.35(13)
C(6)-C(5)-C(11)	108.14(13)	C(10)-C(5)-C(11)	114.03(12)
C(7)-C(6)-C(5)	113.46(13)	C(7)-C(6)-H(6A)	108.9
C(5)-C(6)-H(6A)	108.9	C(7)-C(6)-H(6B)	108.9
C(5)-C(6)-H(6B)	108.9	H(6A)-C(6)-H(6B)	107.7
C(8)-C(7)-C(6)	111.63(15)	C(8)-C(7)-H(7A)	109.3
C(6)-C(7)-H(7A)	109.3	C(8)-C(7)-H(7B)	109.3
C(6)-C(7)-H(7B)	109.3	H(7A)-C(7)-H(7B)	108.0
C(7)-C(8)-C(9)	112.69(14)	C(7)-C(8)-H(8A)	109.1
C(9)-C(8)-H(8A)	109.1	C(7)-C(8)-H(8B)	109.1
C(9)-C(8)-H(8B)	109.1	H(8A)-C(8)-H(8B)	107.8
C(10)-C(9)-C(8)	109.85(13)	C(10)-C(9)-H(9A)	109.7
C(8)-C(9)-H(9A)	109.7	C(10)-C(9)-H(9B)	109.7
C(8)-C(9)-H(9B)	109.7	H(9A)-C(9)-H(9B)	108.2

C(1)-C(10)-C(9)	114.14(13)	C(1)-C(10)-C(5)	116.13(13)
C(9)-C(10)-C(5)	112.69(13)	C(1)-C(10)-H(10)	104.0
C(9)-C(10)-H(10)	104.0	C(5)-C(10)-H(10)	104.0
O(1)-C(11)-C(12)	105.55(14)	O(1)-C(11)-C(5)	112.98(13)
C(12)-C(11)-C(5)	114.57(14)	O(1)-C(11)-H(11)	107.8
C(12)-C(11)-H(11)	107.8	C(5)-C(11)-H(11)	107.8
C(11)-C(12)-H(12A)	109.5	C(11)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5	C(11)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5	H(12B)-C(12)-H(12C)	109.5

Table 6.10 Anisotropic displacement parameters (Å2 x 103) for 193. The anisotropic displacement factor exponent takes the form: -2 gpi2 [h2 a*2 U11 + ... + 2 h k a* b* U]

Atom	U11	U22	U33	U23	U13	U12
O(1)	30(1)	24(1)	38(1)	-6(1)	18(1)	-8(1)
O(2)	23(1)	23(1)	35(1)	1(1)	14(1)	4(1)
C(1)	22(1)	20(1)	29(1)	-3(1)	9(1)	-1(1)
C(2)	27(1)	34(1)	23(1)	-1(1)	5(1)	1(1)
C(3)	25(1)	31(1)	27(1)	6(1)	7(1)	7(1)
C(4)	21(1)	25(1)	27(1)	3(1)	8(1)	6(1)
C(5)	17(1)	18(1)	24(1)	1(1)	7(1)	1(1)
C(6)	26(1)	25(1)	29(1)	1(1)	13(1)	1(1)
C(7)	36(1)	34(1)	26(1)	5(1)	11(1)	0(1)
C(8)	31(1)	27(1)	32(1)	10(1)	8(1)	1(1)
C(9)	24(1)	19(1)	31(1)	3(1)	7(1)	2(1)
C(10)	18(1)	17(1)	26(1)	-1(1)	6(1)	-2(1)
C(11)	23(1)	20(1)	29(1)	-1(1)	10(1)	-2(1)
C(12)	38(1)	25(1)	38(1)	-9(1)	16(1)	-6(1)

Table 6.11 Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2 x 103) for 193.

Atom	x	y	z	U(eq)
H(1)	842	3271	7522	35
H(2)	401	5865	8068	31
H(1A)	2307	7048	8354	28
H(2A)	3272	5025	9553	34
H(2B)	4352	5646	8984	34
H(3A)	2865	2615	8623	33
H(3B)	4496	2789	9102	33
H(4A)	3976	2038	7413	29
H(4B)	4847	3691	7634	29
H(6A)	4349	4956	6150	31
H(6B)	3639	3321	5635	31
H(7A)	2992	5621	4578	38
H(7B)	1663	4771	4784	38
H(8A)	1399	7566	4947	36

H(8B)	2933	7744	5648	36
H(9A)	1419	7889	6641	29
H(9B)	648	6244	6178	29
H(10)	3477	6377	7237	24
H(11)	786	3720	5953	28
H(12A)	2480	874	6229	49
H(12B)	1836	1801	5217	49
H(12C)	850	815	5732	49

Table 6.12 Dihedral angles [o] for 193.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
O(2) - C(1) - C(2) - C(3)	69.28(17)
C(10) - C(1) - C(2) - C(3)	-55.33(18)
C(1) - C(2) - C(3) - C(4)	55.37(19)
C(2) - C(3) - C(4) - C(5)	-53.0(2)
C(3) - C(4) - C(5) - C(6)	161.48(14)
C(3) - C(4) - C(5) - C(10)	47.97(18)
C(3) - C(4) - C(5) - C(11)	-78.97(18)
C(4) - C(5) - C(6) - C(7)	-174.01(14)
C(10) - C(5) - C(6) - C(7)	-58.25(17)
C(11) - C(5) - C(6) - C(7)	63.83(18)
C(5) - C(6) - C(7) - C(8)	55.1(2)
C(6) - C(7) - C(8) - C(9)	-50.4(2)
C(7) - C(8) - C(9) - C(10)	52.46(19)
O(2) - C(1) - C(10) - C(9)	65.18(17)
C(2) - C(1) - C(10) - C(9)	-172.67(14)
O(2) - C(1) - C(10) - C(5)	-68.50(17)
C(2) - C(1) - C(10) - C(5)	53.65(18)
C(8) - C(9) - C(10) - C(1)	165.10(14)
C(8) - C(9) - C(10) - C(5)	-59.63(17)
C(4) - C(5) - C(10) - C(1)	-48.81(17)
C(6) - C(5) - C(10) - C(1)	-164.69(13)
C(11) - C(5) - C(10) - C(1)	77.14(17)
C(4) - C(5) - C(10) - C(9)	176.86(13)
C(6) - C(5) - C(10) - C(9)	60.98(16)
C(11) - C(5) - C(10) - C(9)	-57.19(17)
C(4) - C(5) - C(11) - O(1)	52.51(17)
C(6) - C(5) - C(11) - O(1)	172.32(13)
C(10) - C(5) - C(11) - O(1)	-71.35(17)
C(4) - C(5) - C(11) - C(12)	-68.44(18)
C(6) - C(5) - C(11) - C(12)	51.37(18)
C(10) - C(5) - C(11) - C(12)	167.71(14)

Table 6.13 Crystal data and structure refinement for 266.

Identification code	p10sel2
Empirical formula	$C_{32.75}H_{46.75}Cl_{2.25}N_2O_4$

Formula weight	612.23
Temperature	150(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 14.8975(16)Å α = 90°
	b = 7.3862(4)Å β = 97.729(8)°
	c = 30.776(3)Å γ = 90°
Volume	3355.7(5) $Å^3$
Z	4
Density (calculated)	1.212 Mg/m^3
Absorption coefficient	2.214 mm^{-1}
F(000)	1310
Crystal size	0.35 x 0.10 x 0.06 mm
Theta range for data collection	4.94 to 58.93°
Index ranges	-16<=h<=15; -6<=k<=8; -34<=l<=30
Reflections collected	11535
Independent reflections	4690 [R(int) = 0.1109]
Reflections observed (>2σ)	3004
Data Completeness	0.971
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.59444
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4690 / 10 / 390
Goodness-of-fit on F^2	1.108
Final R indices [I>2σ(I)]	R1 = 0.1043 wR2 = 0.2796
R indices (all data)	R1 = 0.1397 wR2 = 0.3348
Largest diff. peak and hole	0.752 and -0.511 $eÅ^{-3}$

Table 6.14 Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å2 x 103) for 266. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Cl(1)	7903(2)	2378(3)	1804(1)	71(1)
Cl(3)	9010(2)	-637(4)	1598(1)	58(1)
Cl(2)	8030(3)	-678(5)	2359(1)	76(1)
O(1)	1602(2)	248(4)	1464(1)	39(1)
O(2)	2027(2)	-2654(4)	2088(1)	43(1)
N(1)	2235(3)	1854(5)	2033(1)	36(1)
C(1)	2192(3)	299(6)	1832(2)	32(1)
C(2)	1609(4)	2924(7)	1763(2)	44(2)
C(3)	1234(4)	1968(6)	1418(2)	40(1)
C(4)	2693(3)	-1407(6)	1980(2)	34(1)
C(5)	3205(4)	-2255(6)	1621(2)	42(1)
C(6)	3654(4)	-4040(6)	1795(2)	48(2)
C(7)	4472(4)	-3735(7)	2128(2)	50(2)
C(8)	5157(4)	-2561(7)	1945(2)	52(2)

C(9)	4775(4)	-728(6)	1766(2)	45(2)
C(10)	5489(4)	185(8)	1516(2)	56(2)
C(11)	5150(4)	1876(8)	1262(2)	62(2)
C(12)	4310(5)	1456(9)	948(2)	67(2)
C(13)	3566(4)	624(7)	1180(2)	50(2)
C(14)	3921(4)	-1088(7)	1442(2)	44(1)
C(15)	4608(4)	546(6)	2138(2)	45(2)
C(16)	4990(5)	571(8)	2546(2)	64(2)
C(17)	8525(7)	460(11)	1996(3)	81(3)
O(1A)	53(2)	5221(4)	1057(1)	41(1)
O(2A)	10(2)	2326(4)	424(1)	38(1)
N(1A)	-198(3)	6865(5)	449(2)	37(1)
C(1A)	-309(3)	5304(6)	632(2)	35(1)
C(2A)	279(4)	7899(6)	788(2)	40(1)
C(3A)	435(4)	6913(6)	1148(2)	41(1)
C(4A)	-709(3)	3612(6)	415(2)	34(1)
C(5A)	-1484(4)	2800(6)	634(2)	40(1)
C(6A)	-1765(4)	948(6)	429(2)	46(2)
C(7A)	-2288(4)	1163(7)	-31(2)	48(2)
C(8A)	-3115(4)	2333(7)	-23(2)	49(2)
C(9A)	-2894(4)	4223(6)	178(2)	44(1)
C(10A)	-3809(4)	5149(8)	239(2)	53(2)
C(11A)	-3684(4)	6903(8)	505(2)	58(2)
C(12A)	-3111(4)	6611(8)	947(2)	62(2)
C(13A)	-2198(4)	5756(7)	895(2)	47(2)
C(14A)	-2328(4)	3975(6)	633(2)	40(1)
C(15A)	-2414(4)	5422(7)	-120(2)	45(2)
C(16A)	-2417(5)	5261(8)	-547(2)	61(2)
Cl(2A)	7901(8)	-1533(15)	2118(4)	90(3)
Cl(3A)	9380(9)	40(20)	1740(5)	113(5)

Table 6.15 Bond lengths [Å] and angles [o] for 266.

Cl(1)-C(17)	1.752(8)	Cl(3)-C(17)	1.708(8)
Cl(2)-C(17)	1.649(8)	O(1)-C(1)	1.338(6)
O(1)-C(3)	1.383(6)	O(2)-C(4)	1.425(6)
O(2)-H(2)	0.8400	N(1)-C(1)	1.302(6)
N(1)-C(2)	1.405(7)	C(1)-C(4)	1.503(6)
C(2)-C(3)	1.335(8)	C(2)-H(2C)	0.9500
C(3)-H(3)	0.9500	C(4)-C(5)	1.557(8)
C(4)-H(4)	1.0000	C(5)-C(14)	1.531(8)
C(5)-C(6)	1.542(7)	C(5)-H(5)	1.0000
C(6)-C(7)	1.500(8)	C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900	C(7)-C(8)	1.504(8)
C(7)-H(7A)	0.9900	C(7)-H(7B)	0.9900
C(8)-C(9)	1.541(7)	C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900	C(9)-C(15)	1.527(8)
C(9)-C(14)	1.532(8)	C(9)-C(10)	1.550(8)

C(10)-C(11)	1.523(8)	C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900	C(11)-C(12)	1.506(10)
C(11)-H(11A)	0.9900	C(11)-H(11B)	0.9900
C(12)-C(13)	1.527(9)	C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900	C(13)-C(14)	1.553(7)
C(13)-H(13A)	0.9900	C(13)-H(13B)	0.9900
C(14)-H(14)	1.0000	C(15)-C(16)	1.308(8)
C(15)-H(15)	0.9500	C(16)-H(16A)	0.9500
C(16)-H(16B)	0.9500	C(17)-Cl(3A)	1.615(12)
C(17)-Cl(2A)	1.808(12)	C(17)-H(17)	1.0000
O(1A)-C(1A)	1.349(6)	O(1A)-C(3A)	1.386(6)
O(2A)-C(4A)	1.430(5)	O(2A)-H(2A)	0.8400
N(1A)-C(1A)	1.303(6)	N(1A)-C(2A)	1.406(7)
C(1A)-C(4A)	1.501(6)	C(2A)-C(3A)	1.321(8)
C(2A)-H(2B)	0.9500	C(3A)-H(3A)	0.9500
C(4A)-C(5A)	1.535(8)	C(4A)-H(4A)	1.0000
C(5A)-C(14A)	1.527(7)	C(5A)-C(6A)	1.540(7)
C(5A)-H(5A)	1.0000	C(6A)-C(7A)	1.532(8)
C(6A)-H(6A1)	0.9900	C(6A)-H(6A2)	0.9900
C(7A)-C(8A)	1.508(8)	C(7A)-H(7A1)	0.9900
C(7A)-H(7A2)	0.9900	C(8A)-C(9A)	1.544(7)
C(8A)-H(8A1)	0.9900	C(8A)-H(8A2)	0.9900
C(9A)-C(15A)	1.521(8)	C(9A)-C(14A)	1.546(8)
C(9A)-C(10A)	1.559(8)	C(10A)-C(11A)	1.530(8)
C(10A)-H(10C)	0.9900	C(10A)-H(10D)	0.9900
C(11A)-C(12A)	1.520(10)	C(11A)-H(11C)	0.9900
C(11A)-H(11D)	0.9900	C(12A)-C(13A)	1.528(8)
C(12A)-H(12C)	0.9900	C(12A)-H(12D)	0.9900
C(13A)-C(14A)	1.541(7)	C(13A)-H(13C)	0.9900
C(13A)-H(13D)	0.9900	C(14A)-H(14A)	1.0000
C(15A)-C(16A)	1.320(8)	C(15A)-H(15A)	0.9500
C(16A)-H(16C)	0.9500	C(16A)-H(16D)	0.9500
C(1)-O(1)-C(3)	105.5(4)	C(4)-O(2)-H(2)	109.5
C(1)-N(1)-C(2)	103.3(4)	N(1)-C(1)-O(1)	114.3(4)
N(1)-C(1)-C(4)	127.3(4)	O(1)-C(1)-C(4)	118.4(4)
C(3)-C(2)-N(1)	110.3(4)	C(3)-C(2)-H(2C)	124.9
N(1)-C(2)-H(2C)	124.9	C(2)-C(3)-O(1)	106.6(4)
C(2)-C(3)-H(3)	126.7	O(1)-C(3)-H(3)	126.7
O(2)-C(4)-C(1)	106.3(4)	O(2)-C(4)-C(5)	109.2(4)
C(1)-C(4)-C(5)	113.1(4)	O(2)-C(4)-H(4)	109.4
C(1)-C(4)-H(4)	109.4	C(5)-C(4)-H(4)	109.4
C(14)-C(5)-C(6)	108.4(4)	C(14)-C(5)-C(4)	117.5(4)
C(6)-C(5)-C(4)	109.2(5)	C(14)-C(5)-H(5)	107.1
C(6)-C(5)-H(5)	107.1	C(4)-C(5)-H(5)	107.1
C(7)-C(6)-C(5)	112.5(4)	C(7)-C(6)-H(6A)	109.1
C(5)-C(6)-H(6A)	109.1	C(7)-C(6)-H(6B)	109.1
C(5)-C(6)-H(6B)	109.1	H(6A)-C(6)-H(6B)	107.8
C(6)-C(7)-C(8)	111.2(5)	C(6)-C(7)-H(7A)	109.4

C(8)-C(7)-H(7A)	109.4	C(6)-C(7)-H(7B)	109.4
C(8)-C(7)-H(7B)	109.4	H(7A)-C(7)-H(7B)	108.0
C(7)-C(8)-C(9)	113.8(5)	C(7)-C(8)-H(8A)	108.8
C(9)-C(8)-H(8A)	108.8	C(7)-C(8)-H(8B)	108.8
C(9)-C(8)-H(8B)	108.8	H(8A)-C(8)-H(8B)	107.7
C(15)-C(9)-C(14)	113.0(5)	C(15)-C(9)-C(8)	111.3(5)
C(14)-C(9)-C(8)	108.3(4)	C(15)-C(9)-C(10)	107.3(4)
C(14)-C(9)-C(10)	108.4(5)	C(8)-C(9)-C(10)	108.4(4)
C(11)-C(10)-C(9)	114.2(5)	C(11)-C(10)-H(10A)	108.7
C(9)-C(10)-H(10A)	108.7	C(11)-C(10)-H(10B)	108.7
C(9)-C(10)-H(10B)	108.7	H(10A)-C(10)-H(10B)	107.6
C(12)-C(11)-C(10)	110.5(5)	C(12)-C(11)-H(11A)	109.6
C(10)-C(11)-H(11A)	109.6	C(12)-C(11)-H(11B)	109.6
C(10)-C(11)-H(11B)	109.6	H(11A)-C(11)-H(11B)	108.1
C(11)-C(12)-C(13)	112.0(6)	C(11)-C(12)-H(12A)	109.2
C(13)-C(12)-H(12A)	109.2	C(11)-C(12)-H(12B)	109.2
C(13)-C(12)-H(12B)	109.2	H(12A)-C(12)-H(12B)	107.9
C(12)-C(13)-C(14)	110.6(5)	C(12)-C(13)-H(13A)	109.5
C(14)-C(13)-H(13A)	109.5	C(12)-C(13)-H(13B)	109.5
C(14)-C(13)-H(13B)	109.5	H(13A)-C(13)-H(13B)	108.1
C(5)-C(14)-C(9)	114.9(5)	C(5)-C(14)-C(13)	116.1(4)
C(9)-C(14)-C(13)	113.0(4)	C(5)-C(14)-H(14)	103.6
C(9)-C(14)-H(14)	103.6	C(13)-C(14)-H(14)	103.6
C(16)-C(15)-C(9)	129.4(5)	C(16)-C(15)-H(15)	115.3
C(9)-C(15)-H(15)	115.3	C(15)-C(16)-H(16A)	120.0
C(15)-C(16)-H(16B)	120.0	H(16A)-C(16)-H(16B)	120.0
Cl(3A)-C(17)-Cl(2)	133.4(7)	Cl(3A)-C(17)-Cl(3)	28.6(6)
Cl(2)-C(17)-Cl(3)	121.0(5)	Cl(3A)-C(17)-Cl(1)	114.0(7)
Cl(2)-C(17)-Cl(1)	112.1(5)	Cl(3)-C(17)-Cl(1)	113.4(5)
Cl(3A)-C(17)-Cl(2A)	114.0(8)	Cl(2)-C(17)-Cl(2A)	32.3(4)
Cl(3)-C(17)-Cl(2A)	92.4(6)	Cl(1)-C(17)-Cl(2A)	117.7(7)
Cl(3A)-C(17)-H(17)	74.4	Cl(2)-C(17)-H(17)	102.4
Cl(3)-C(17)-H(17)	102.4	Cl(1)-C(17)-H(17)	102.4
Cl(2A)-C(17)-H(17)	127.0	C(1A)-O(1A)-C(3A)	104.8(4)
C(4A)-O(2A)-H(2A)	109.5	C(1A)-N(1A)-C(2A)	104.0(4)
N(1A)-C(1A)-O(1A)	113.7(4)	N(1A)-C(1A)-C(4A)	127.7(5)
O(1A)-C(1A)-C(4A)	118.4(4)	C(3A)-C(2A)-N(1A)	109.7(4)
C(3A)-C(2A)-H(2B)	125.1	N(1A)-C(2A)-H(2B)	125.1
C(2A)-C(3A)-O(1A)	107.8(5)	C(2A)-C(3A)-H(3A)	126.1
O(1A)-C(3A)-H(3A)	126.1	O(2A)-C(4A)-C(1A)	107.1(4)
O(2A)-C(4A)-C(5A)	109.8(4)	C(1A)-C(4A)-C(5A)	114.0(4)
O(2A)-C(4A)-H(4A)	108.6	C(1A)-C(4A)-H(4A)	108.6
C(5A)-C(4A)-H(4A)	108.6	C(14A)-C(5A)-C(4A)	116.4(4)
C(14A)-C(5A)-C(6A)	109.0(4)	C(4A)-C(5A)-C(6A)	110.3(5)
C(14A)-C(5A)-H(5A)	106.9	C(4A)-C(5A)-H(5A)	106.9
C(6A)-C(5A)-H(5A)	106.9	C(7A)-C(6A)-C(5A)	111.3(4)
C(7A)-C(6A)-H(6A1)	109.4	C(5A)-C(6A)-H(6A1)	109.4
C(7A)-C(6A)-H(6A2)	109.4	C(5A)-C(6A)-H(6A2)	109.4

H(6A1)-C(6A)-H(6A2)	108.0	C(8A)-C(7A)-C(6A)	111.0(5)
C(8A)-C(7A)-H(7A1)	109.4	C(6A)-C(7A)-H(7A1)	109.4
C(8A)-C(7A)-H(7A2)	109.4	C(6A)-C(7A)-H(7A2)	109.4
H(7A1)-C(7A)-H(7A2)	108.0	C(7A)-C(8A)-C(9A)	113.2(5)
C(7A)-C(8A)-H(8A1)	108.9	C(9A)-C(8A)-H(8A1)	108.9
C(7A)-C(8A)-H(8A2)	108.9	C(9A)-C(8A)-H(8A2)	108.9
H(8A1)-C(8A)-H(8A2)	107.7	C(15A)-C(9A)-C(8A)	112.2(5)
C(15A)-C(9A)-C(14A)	111.8(4)	C(8A)-C(9A)-C(14A)	108.5(4)
C(15A)-C(9A)-C(10A)	107.9(4)	C(8A)-C(9A)-C(10A)	107.6(4)
C(14A)-C(9A)-C(10A)	108.8(5)	C(11A)-C(10A)-C(9A)	113.0(5)
C(11A)-C(10A)-H(10C)	109.0	C(9A)-C(10A)-H(10C)	109.0
C(11A)-C(10A)-H(10D)	109.0	C(9A)-C(10A)-H(10D)	109.0
H(10C)-C(10A)-H(10D)	107.8	C(12A)-C(11A)-C(10A)	111.8(5)
C(12A)-C(11A)-H(11C)	109.3	C(10A)-C(11A)-H(11C)	109.3
C(12A)-C(11A)-H(11D)	109.3	C(10A)-C(11A)-H(11D)	109.3
H(11C)-C(11A)-H(11D)	107.9	C(11A)-C(12A)-C(13A)	111.4(6)
C(11A)-C(12A)-H(12C)	109.3	C(13A)-C(12A)-H(12C)	109.3
C(11A)-C(12A)-H(12D)	109.3	C(13A)-C(12A)-H(12D)	109.3
H(12C)-C(12A)-H(12D)	108.0	C(12A)-C(13A)-C(14A)	110.9(5)
C(12A)-C(13A)-H(13C)	109.5	C(14A)-C(13A)-H(13C)	109.5
C(12A)-C(13A)-H(13D)	109.5	C(14A)-C(13A)-H(13D)	109.5
H(13C)-C(13A)-H(13D)	108.0	C(5A)-C(14A)-C(13A)	116.1(4)
C(5A)-C(14A)-C(9A)	114.7(5)	C(13A)-C(14A)-C(9A)	112.8(4)
C(5A)-C(14A)-H(14A)	103.8	C(13A)-C(14A)-H(14A)	103.8
C(9A)-C(14A)-H(14A)	103.8	C(16A)-C(15A)-C(9A)	127.5(5)
C(16A)-C(15A)-H(15A)	116.2	C(9A)-C(15A)-H(15A)	116.2
C(15A)-C(16A)-H(16C)	120.0	C(15A)-C(16A)-H(16D)	120.0
H(16C)-C(16A)-H(16D)	120.0		

Table 6.16 Anisotropic displacement parameters (Å2 x 103) for 266. The anisotropic displacement factor exponent takes the form: -2 gpi2 [h2 a*2 U11 + ... + 2 h k a* b* U].

Atom	U11	U22	U33	U23	U13	U12
Cl(1)	78(2)	61(1)	76(2)	9(1)	14(1)	19(1)
Cl(3)	85(2)	38(1)	48(2)	-2(1)	1(2)	12(1)
Cl(2)	84(2)	73(2)	72(2)	34(2)	12(2)	-6(2)
O(1)	48(2)	18(2)	47(2)	-2(2)	-13(2)	4(1)
O(2)	54(2)	25(2)	45(2)	7(2)	-13(2)	-10(2)
N(1)	43(3)	20(2)	43(3)	-2(2)	-6(2)	5(2)
C(1)	27(3)	27(3)	37(3)	0(2)	-9(2)	0(2)
C(2)	50(3)	26(3)	50(4)	0(2)	-14(3)	3(2)
C(3)	47(3)	23(3)	45(3)	3(2)	-10(3)	4(2)
C(4)	45(3)	15(2)	38(3)	-1(2)	-14(2)	-3(2)
C(5)	47(3)	24(3)	48(4)	-4(2)	-17(3)	2(2)
C(6)	51(4)	23(3)	67(4)	-5(3)	-8(3)	6(2)
C(7)	56(4)	23(3)	66(4)	8(3)	-12(3)	7(2)
C(8)	48(4)	35(3)	68(5)	0(3)	-8(3)	8(2)
C(9)	41(3)	27(3)	64(4)	-1(2)	-6(3)	5(2)

C(10)	49(4)	46(3)	74(5)	1(3)	7(3)	5(3)
C(11)	65(4)	49(4)	76(5)	19(3)	23(4)	9(3)
C(12)	67(5)	64(4)	72(5)	25(4)	18(4)	14(3)
C(13)	59(4)	40(3)	48(4)	1(3)	-2(3)	8(3)
C(14)	48(3)	33(3)	47(4)	-6(2)	-3(3)	11(2)
C(15)	42(3)	29(3)	60(4)	1(3)	-6(3)	-1(2)
C(16)	68(5)	53(4)	64(5)	-12(3)	-15(4)	7(3)
C(17)	94(8)	90(7)	59(7)	9(5)	15(6)	16(6)
O(1A)	48(2)	22(2)	46(2)	1(2)	-15(2)	-3(2)
O(2A)	41(2)	26(2)	44(2)	2(2)	-4(2)	8(1)
N(1A)	45(3)	21(2)	43(3)	3(2)	-6(2)	-1(2)
C(1A)	33(3)	26(3)	43(3)	1(2)	-2(2)	2(2)
C(2A)	42(3)	19(2)	55(4)	2(2)	-7(3)	0(2)
C(3A)	50(3)	22(3)	45(4)	-5(2)	-14(3)	-4(2)
C(4A)	40(3)	15(2)	40(3)	-2(2)	-13(2)	5(2)
C(5A)	45(3)	25(2)	44(3)	3(2)	-13(3)	-6(2)
C(6A)	55(4)	18(2)	60(4)	-1(2)	-12(3)	-5(2)
C(7A)	55(4)	26(3)	59(4)	-10(3)	-8(3)	-6(2)
C(8A)	54(4)	34(3)	52(4)	5(3)	-19(3)	-8(3)
C(9A)	39(3)	27(3)	61(4)	5(2)	-10(3)	-1(2)
C(10A)	44(4)	44(3)	68(4)	-1(3)	-3(3)	-4(3)
C(11A)	46(4)	43(3)	86(5)	0(3)	14(3)	6(3)
C(12A)	57(4)	49(4)	82(5)	-17(3)	12(4)	7(3)
C(13A)	40(3)	34(3)	64(4)	-5(3)	0(3)	1(2)
C(14A)	44(3)	26(3)	48(3)	-1(2)	3(3)	-2(2)
C(15A)	46(3)	29(3)	52(4)	9(2)	-16(3)	6(2)
C(16A)	71(5)	51(4)	54(4)	10(3)	-13(3)	1(3)

Table 6.17 Hydrogen coordinates (x 104) and isotropic displacement parameters (Å2 x 103) for 266.

Atom	x	y	z	U(eq)
H(2)	2145	-2950	2353	52
H(2C)	1472	4151	1819	53
H(3)	800	2388	1185	48
H(4)	3133	-1147	2247	41
H(5)	2740	-2572	1367	50
H(6A)	3207	-4771	1929	58
H(6B)	3834	-4739	1546	58
H(7A)	4752	-4915	2218	60
H(7B)	4285	-3148	2391	60
H(8A)	5396	-3225	1706	63
H(8B)	5670	-2334	2179	63
H(10A)	6023	512	1728	68
H(10B)	5690	-704	1308	68
H(11A)	5013	2829	1469	75
H(11B)	5628	2340	1097	75
H(12A)	4467	605	721	80

H(12B)	4081	2585	799	80
H(13A)	3043	294	961	60
H(13B)	3358	1524	1383	60
H(14)	4143	-1878	1214	52
H(15)	4163	1453	2061	54
H(16A)	5442	-296	2646	77
H(16B)	4815	1455	2743	77
H(17)	9062	1002	2181	97
H(2A)	289	2499	208	45
H(2B)	462	9121	761	48
H(3A)	753	7295	1421	50
H(4A)	-942	3894	102	40
H(5A)	-1239	2573	948	48
H(6A1)	-1217	206	414	56
H(6A2)	-2149	306	619	56
H(7A1)	-1888	1717	-227	58
H(7A2)	-2475	-45	-151	58
H(8A1)	-3539	1709	149	59
H(8A2)	-3424	2482	-326	59
H(10C)	-4147	5419	-53	63
H(10D)	-4177	4296	389	63
H(11C)	-3389	7819	337	70
H(11D)	-4285	7378	552	70
H(12C)	-3442	5814	1130	75
H(12D)	-3010	7788	1099	75
H(13C)	-1859	5512	1188	56
H(13D)	-1838	6612	741	56
H(14A)	-2729	3238	800	47
H(15A)	-2071	6400	18	53
H(16C)	-2748	4308	-702	73
H(16D)	-2089	6097	-699	73

Table 6.18 Dihedral angles [o] for 266.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(2) - N(1) - C(1) - O(1)	-0.3(6)
C(2) - N(1) - C(1) - C(4)	-177.4(5)
C(3) - O(1) - C(1) - N(1)	1.1(6)
C(3) - O(1) - C(1) - C(4)	178.4(4)
C(1) - N(1) - C(2) - C(3)	-0.6(6)
N(1) - C(2) - C(3) - O(1)	1.2(6)
C(1) - O(1) - C(3) - C(2)	-1.3(6)
N(1) - C(1) - C(4) - O(2)	111.7(5)
O(1) - C(1) - C(4) - O(2)	-65.3(6)
N(1) - C(1) - C(4) - C(5)	-128.6(5)
O(1) - C(1) - C(4) - C(5)	54.5(6)
O(2) - C(4) - C(5) - C(14)	177.0(4)
C(1) - C(4) - C(5) - C(14)	58.9(6)

O(2) - C(4) - C(5) - C(6)	-59.1(5)
C(1) - C(4) - C(5) - C(6)	-177.1(4)
C(14) - C(5) - C(6) - C(7)	55.1(7)
C(4) - C(5) - C(6) - C(7)	-74.0(6)
C(5) - C(6) - C(7) - C(8)	-56.3(7)
C(6) - C(7) - C(8) - C(9)	55.4(7)
C(7) - C(8) - C(9) - C(15)	72.4(6)
C(7) - C(8) - C(9) - C(14)	-52.5(7)
C(7) - C(8) - C(9) - C(10)	-169.9(5)
C(15) - C(9) - C(10) - C(11)	-68.5(7)
C(14) - C(9) - C(10) - C(11)	53.9(6)
C(8) - C(9) - C(10) - C(11)	171.2(5)
C(9) - C(10) - C(11) - C(12)	-55.9(7)
C(10) - C(11) - C(12) - C(13)	55.7(7)
C(11) - C(12) - C(13) - C(14)	-55.5(7)
C(6) - C(5) - C(14) - C(9)	-54.9(6)
C(4) - C(5) - C(14) - C(9)	69.4(6)
C(6) - C(5) - C(14) - C(13)	170.1(5)
C(4) - C(5) - C(14) - C(13)	-65.6(6)
C(15) - C(9) - C(14) - C(5)	-70.5(6)
C(8) - C(9) - C(14) - C(5)	53.3(6)
C(10) - C(9) - C(14) - C(5)	170.7(4)
C(15) - C(9) - C(14) - C(13)	65.9(6)
C(8) - C(9) - C(14) - C(13)	-170.3(5)
C(10) - C(9) - C(14) - C(13)	-52.9(6)
C(12) - C(13) - C(14) - C(5)	-169.1(5)
C(12) - C(13) - C(14) - C(9)	55.0(7)
C(14) - C(9) - C(15) - C(16)	147.0(6)
C(8) - C(9) - C(15) - C(16)	24.8(8)
C(10) - C(9) - C(15) - C(16)	-93.6(7)
C(2A) - N(1A) - C(1A) - O(1A)	-0.2(6)
C(2A) - N(1A) - C(1A) - C(4A)	-174.4(5)
C(3A) - O(1A) - C(1A) - N(1A)	-0.3(6)
C(3A) - O(1A) - C(1A) - C(4A)	174.5(4)
C(1A) - N(1A) - C(2A) - C(3A)	0.7(6)
N(1A) - C(2A) - C(3A) - O(1A)	-0.9(6)
C(1A) - O(1A) - C(3A) - C(2A)	0.7(6)
N(1A) - C(1A) - C(4A) - O(2A)	111.5(6)
O(1A) - C(1A) - C(4A) - O(2A)	-62.4(6)
N(1A) - C(1A) - C(4A) - C(5A)	-126.8(6)
O(1A) - C(1A) - C(4A) - C(5A)	59.2(6)
O(2A) - C(4A) - C(5A) - C(14A)	-177.3(4)
C(1A) - C(4A) - C(5A) - C(14A)	62.6(6)
O(2A) - C(4A) - C(5A) - C(6A)	-52.4(5)
C(1A) - C(4A) - C(5A) - C(6A)	-172.6(4)
C(14A) - C(5A) - C(6A) - C(7A)	55.8(6)
C(4A) - C(5A) - C(6A) - C(7A)	-73.1(6)
C(5A) - C(6A) - C(7A) - C(8A)	-57.4(6)

C(6A) - C(7A) - C(8A) - C(9A)	56.5(6)
C(7A) - C(8A) - C(9A) - C(15A)	71.0(6)
C(7A) - C(8A) - C(9A) - C(14A)	-53.0(7)
C(7A) - C(8A) - C(9A) - C(10A)	-170.5(5)
C(15A) - C(9A) - C(10A) - C(11A)	-68.3(7)
C(8A) - C(9A) - C(10A) - C(11A)	170.5(5)
C(14A) - C(9A) - C(10A) - C(11A)	53.2(6)
C(9A) - C(10A) - C(11A) - C(12A)	-54.7(7)
C(10A) - C(11A) - C(12A) - C(13A)	55.0(7)
C(11A) - C(12A) - C(13A) - C(14A)	-55.5(7)
C(4A) - C(5A) - C(14A) - C(13A)	-64.3(7)
C(6A) - C(5A) - C(14A) - C(13A)	170.2(5)
C(4A) - C(5A) - C(14A) - C(9A)	70.0(6)
C(6A) - C(5A) - C(14A) - C(9A)	-55.5(6)
C(12A) - C(13A) - C(14A) - C(5A)	-168.5(5)
C(12A) - C(13A) - C(14A) - C(9A)	56.3(7)
C(15A) - C(9A) - C(14A) - C(5A)	-70.8(5)
C(8A) - C(9A) - C(14A) - C(5A)	53.4(6)
C(10A) - C(9A) - C(14A) - C(5A)	170.1(4)
C(15A) - C(9A) - C(14A) - C(13A)	65.0(6)
C(8A) - C(9A) - C(14A) - C(13A)	-170.8(5)
C(10A) - C(9A) - C(14A) - C(13A)	-54.1(6)
C(8A) - C(9A) - C(15A) - C(16A)	21.7(8)
C(14A) - C(9A) - C(15A) - C(16A)	143.8(6)
C(10A) - C(9A) - C(15A) - C(16A)	-96.6(7)